Hospitalisation in Older Patients due to Adverse Drug Reactions

by

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B. Pharm, M. Pharm

A thesis submitted in fulfillment of the requirements for the degree of

Doctor of Philosophy

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Declaration of Originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving Tasmanian patients was conducted under the approval of the Tasmania Health and Medical Human Research Ethics Committee: Approval numbers H0013773, H0015152, and H0015610.

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Statement of Co-Authorship

Given that this thesis is presented as a sequence of papers, either published, in press or submitted, statement of co-authorship is provided for each chapter. Due to this thesis format, some repetition is expected.

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Publications and Presentations

All publications and presentations listed resulted from work described in this thesis.

A. Publications (Peer-Reviewed Journal)

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1. Parameswaran Nair N, Chalmers L, Bereznicki BJ, Curtain C, Connolly M, Bereznicki LR. Repeat Adverse Drug Reactions-related Hospital Admissions in Elderly Australians. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 22nd Annual International Meeting 2017, Boston, USA (Poster presentation).
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4. Parameswaran Nair N, Chalmers L, Bereznicki BJ, Peterson GM, Castelino RL, Bereznicki LR. Predicting Hospitalisation due to Adverse Drug Reactions. The University of Tasmania, Graduate Research Conference 2014, Hobart, Australia (Poster presentation).
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C. Conference Publications

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2. Parameswaran Nair N, Chalmers L, Bereznicki BJ, Castelino RL, Peterson GM, Curtain C, Connolly M, Bereznicki LR. Development of a Score to Predict Hospitalisation due to Adverse Drug Reactions in Older Patients. Research in Social and Administrative Pharmacy 2016; 12(5): e29-e30.

D. Award/Grants/Scholarships

1. A scientific paper entitled 'Repeat Adverse Drug Reaction-related Hospital Admissions in Elderly Australians' was awarded the best student research poster presentation (first prize) in the poster session of ISPOR 22nd Annual International Meeting, 20-24 May 2017, Boston, USA.
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We the undersigned agree with the above stated "proportion of work undertaken" for each of the above published or under review peer-reviewed manuscripts contributing to this thesis:

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Glossary of Abbreviations

Abbreviation	Meaning
ACEI	Angiotensin converting enzyme inhibitor
ADR	Adverse drug reaction
ADE	Adverse drug event
AE	Adverse event
AOR	Adjusted odds ratio
ARB	Angiotensin receptor blocker
AUC	Area under the curve
ATC	Anatomical Therapeutic and Chemical
CCI	Charlson comorbidity index
CDSS	Clinical decision support system
COPD	Chronic obstructive pulmonary disease
CPOE	Computerised physician order entry
CI	Confidence interval
DDI	Drug-drug interaction
DRP	Drug-related problem
ED	Emergency department
eGFR	Estimated glomerular filtration rate
GP	General practitioner
HMR	Home medicines review
HR	Hazard ratio
ICD	International Classification of Diseases

Abbreviation	Meaning
IQR	Interquartile range
LGH	Launceston General Hospital
ME	Medication error
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
OTC	Over-the-counter
PADR-EC	Prediction of hospitalisation due to adverse drug reactions in elderly community-dwelling patients
PIM	Potentially inappropriate medication
PPV	Positive predictive value
RAS	Renin-angiotensin system
RHH	Royal Hobart Hospital
ROC	Receiver operator characteristic
SD	Standard deviation
STOPP	Screening Tool of Older Person's Prescriptions
UK	United Kingdom
US	United States
WHO	World Health Organisation

Abstract

Medication safety at various stages of the patient journey continues to be a significant problem. The increasingly ageing population worldwide, together with the growing use of multiple medications, leads to an increased risk of medication-related problems. In Australia, the proportion of all hospital admissions that are medication-related is between 2% and 3%. Adverse drug reactions (ADRs) are the most common medication-related problems causing significant morbidity and mortality. Based on data collected from general practitioners' encounters in 2003 and 2004 in Australia, ADRs represented the most common adverse drug event in the community (72%). Older patients are particularly susceptible to ADRs due to multiple comorbidities, cognitive and functional impairment, a high prevalence of polypharmacy, and age-related changes in pharmacokinetics and pharmacodynamics. Of particular concern are ADR-related hospital admissions which are one of the main reasons for hospitalisation in older patients living in the community. More than half of these ADR-related admissions are considered preventable. Even though several methods of ADR identification exist, prospective and intensive monitoring methods using patient interviews usually have the highest ADR detection rate and allow more accurate recording of both drug history and symptoms for assessing the causality of ADRs. A prospective cross-sectional survey in Australia (1998) estimated that 13.3% of elderly admissions to medical wards were ADR-related. A recent meta-analysis found that one in ten hospital admissions in older patients were due to ADRs. Despite the current efforts to identify and prevent ADRs, the burden of ADRs is continuing. A secondary data analysis of case series in Australia (1981-2002) found that hospital admissions due to ADRs in elderly patients had increased despite programs to promote rational and safer use of medicines. In addition to this burden, ADRs that result in

hospitalisation in patients with a history of ADR-related hospitalisation, or 'repeat ADRs' are also increasingly common and an important contributor to the burden of ADRs. A population-based longitudinal study (1980-2003) in Australia found that repeat ADR-related hospitalisations had increased faster than first-time ADRs in the elderly since 1980 and were responsible for 30.3% of all ADR-related admissions in 2003.

Hence, strategies to reduce the risk of ADR-related admissions, as well as repeat admissions due to ADRs, are required to reduce the global burden of ADR-related admissions, especially in the elderly. While various strategies including medication review, avoiding use of potentially inappropriate medications, computer-based prescribing systems, and comprehensive geriatric assessment have been suggested, health professionals are not able to easily identify elderly community-dwelling outpatients who are at high risk of being hospitalised due to an ADR. To our knowledge, there are no empirical data that allow stratification of community-dwelling older people according to the likelihood of ADRs leading to hospital admission. A tool that focusses on ADRs as a cause of hospitalisation could potentially be used in primary care and at the point of hospital discharge to prioritise primary care-based medication management services to prevent ADR-related morbidity and mortality in patients at the highest risk of such events. Furthermore, given the scarcity of ADR-related hospital admissions data in the elderly identified using prospective intensive monitoring, and the lack of recent data from Australia, more recent estimates of the burden of ADRs are needed.

The overall objective of the body of work contained in this thesis was to fill these gaps in the literature by developing a practical, efficient and simple method of identifying people 65 years and older who are at high risk of experiencing an ADR leading to hospitalisation. The specific aims were:

1. To investigate the proportion, clinical characteristics, causality, severity, preventability, and outcome of ADR-related admissions in older patients admitted to medical wards of two Tasmanian hospitals.
2. To develop and validate a prediction model for ADR-related hospitalisation in patients aged ≥65 years.
3. To investigate the occurrence of repeat ADR-related admissions in elderly patients within 12 months of a hospital admission to a medical ward due to an ADR.
4. To investigate the utility of a validated ADR score in identifying patients at higher risk of a repeat ADR-related hospitalisation.
5. To compare the rates of ADR-related hospitalisations using different methods of detection.

In order to achieve these aims, we conducted a prospective cross-sectional study in the medical wards of two hospitals in Tasmania, Australia: the Royal Hobart Hospital (RHH) and the Launceston General Hospital (LGH). ADR-related hospital admission was determined by clinical pharmacists through expert consensus from comprehensive reviews of medical records and patient interviews. The causality, preventability, and severity of each ADR-related admission were assessed. We pooled the data from both hospitals, which allowed us to investigate the extent of the problem by determining the proportion of ADR-related admissions in older patients admitted to Tasmanian hospitals, identifying commonly implicated drugs, and describing the clinical manifestations and outcomes of ADRs. Of 1008 admissions from the pooled analysis of the RHH and LGH data, 18.9% of admissions were potentially related to ADRs categorised as ‘definite, probable or possible’; 88.5% of these admissions were preventable. Cardiovascular

complaints (29.3%) represented the most common ADRs, followed by neuropsychiatric (20%) and renal and genitourinary disorders (15.2%). The most frequently implicated drug classes were diuretics (23.9%), renin–angiotensin system inhibitors (16.4%), β-blocking agents (7.1%), antidepressants (6.9%), and antithrombotic agents (6.9%). ADR severity was rated moderate and severe in 97.9% and 2.1% of admissions, respectively.

A predictive score named the 'PADR-EC score' was developed using the data from the RHH (derivation cohort), and the score was validated using the data from the LGH (validation cohort). In the derivation sample at the RHH, 115 (15%) patients were admitted due to a 'definite or probable' ADR; 92.2% of these admissions were deemed preventable. In the validation sample at the LGH, 30 (12.5%) patients' admissions were related to definite or probable ADRs; 80% of these admissions were deemed preventable. The predictive ability of the score in the derivation sample at the RHH was 0.70 (95% confidence interval (CI), 0.65–0.75) and 0.67 (95% CI 0.56–0.78) in the validation sample at the LGH. The PADR-EC score assigns points to five significant predictors of ADR-related hospitalisation: (i) antihypertensive use (three or five points if 1-2 or ≥3 antihypertensives, respectively), (ii) renal failure (two points), (iii) dementia (two points), (iv) inappropriate anticholinergic use (two points) and (v) drug changes in the preceding three months (two points). These points are summed to produce the final score, with the risk of ADR-related hospitalisation more than three times higher in those with a score ≥6.

After the development and validation of the ADR score, the occurrence of repeat ADR-related admissions was estimated using the data from the RHH participants who had an ADR-related admission and experienced a subsequent admission due to an ADR within 12 months of discharge from their initial index admission. Of the 112 definite or probable ADR-related admissions among the RHH cohort (three patients died during their

index admission), repeat ADR-related admissions occurred in 13.4% (n=15). Patients with a repeat ADR-related admission had significantly higher PADR-EC scores at the discharge of their index admission (median PADR-EC score 7, interquartile range (IQR) 2-11) than patients who did not have a repeat admission due to ADRs (median PADR-EC score 7, IQR 5-7, P=0.034).

Finally, to compare the rates of ADR-related hospitalisations using different methods of detection, we linked the records of patients from the RHH cohort, where clinical pharmacists prospectively identified ADRs, to their hospital administrative data. We then identified patients in the prospective study whose admissions were coded as ADRs using the International Classification of Diseases 10th Revision Australian Modification (ICD-10 AM) codes. We found that only 2.7% of patients were identified as having been admitted due to ADRs using the ICD-10 AM codes compared to the 15% identified by the prospective review.

This body of work has resulted in the development and external validation of a simple and robust approach to identifying community-dwelling elderly patients at risk of hospitalisation due to preventable ADRs. To our knowledge, this approach has never been adopted before in the field of assessing ADR-related admissions in the elderly. Furthermore, our research has identified the extent of the current problem of ADR-related admissions as well as ADR-related repeat admissions in the elderly Tasmanian population. Our study found that almost one in five unplanned overnight hospital admissions to medical wards in elderly Australian patients were related to ADRs. Additionally, our study showed that one in eight elderly patients hospitalised due to an ADR had a repeat admission for ADR within 12 months of discharge. These findings update the existing information on the rate of ADR-related admissions and repeat

admissions in the elderly. More detailed prospective review of admissions gave a clearer understanding of the true number of ADRs for directing appropriate medication management services towards addressing the problem. We suggest that the PADR-EC score has the potential to assist healthcare practitioners at the point of discharge and in primary care to identify those elderly patients for whom intervention may reduce the risk of ADRs and subsequent hospitalisation. Future studies are required to investigate the utility of the PADR-EC score in these settings and thereafter the effectiveness of interventions, such as deprescribing, in reducing the risk of ADR-related admissions in elderly populations.

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THESIS OVERVIEW

1.1. Problem statement

Adverse drug reactions (ADRs) represent a major public health problem causing significant morbidity, mortality, and healthcare costs [1, 2]. ADRs pose a significant risk especially in the elderly because ageing is associated with pharmacokinetic and pharmacodynamic changes, co-administration of multiple medications or polypharmacy, comorbidities, cognitive impairment and functional disability [3, 4]. Of particular concern is the high prevalence of ADRs leading to hospitalisation in the elderly. A large body of research exists regarding the consequences of ADRs causing admissions or repeat admissions to hospital in older adults, and various preventive strategies have been suggested. Despite strategies promoting rational and safer use of medicines such as medication review, avoiding the use of potentially inappropriate medications, using computer-based prescribing systems and comprehensive geriatric assessment [3], the problem of ADRs has persisted [5]. ADR-related admissions and repeat admissions due to ADRs continue to be a leading cause of preventable morbidity and mortality in the older population worldwide [6-8]. One possible solution to this issue is to improve the targeting of medication management services to those at highest risk and to better inform the design of these services through enhancing our understanding of ADRs that lead to hospitalisation. Previous studies suggest that identification of the population at risk of ADRs using a prediction tool may be a useful first step to allow health professionals to target medication management services towards this group, and to put in place strategies to prevent ADRs [9, 10]. However, currently available ADR tools in the elderly are developed for identifying the risk of ADRs occurring during hospitalisation. A tool that

focusses on ADRs as a cause of hospitalisation could potentially be used in primary care and at the point of hospital discharge, to prioritise primary care-based medication management services to prevent ADR-related morbidity and mortality in patients at the highest risk of such events. Furthermore, the scarcity of prospectively identified data, together with a lack of recent Australian data on ADR-related admissions in the elderly, necessitates the estimation of the current burden of ADR-related admissions as well as repeat admissions due to ADRs in the older population. We also need to better understand the risk factors associated with ADR-related hospitalisations, as most of the Australian data has focussed on risk factors derived from administrative databases. Prospective data provides us with a greater range of events, and potentially a better understanding of the risk factors involved.

1.2. Aim and objectives

The overall aim of this thesis was to develop and validate a practical, efficient and simple method of identifying people aged 65 years and older who are at high risk of experiencing an ADR leading to hospitalisation. This aim was addressed through a narrative literature review, and a prospective study involving two Tasmanian hospitals. Data from the prospective study is presented in four separate analyses to address the specific objectives of the work. These objectives were as follows:

1. To investigate the proportion, clinical characteristics, causality, severity, preventability, and outcome of ADR-related admissions in older patients admitted to medical wards of two Tasmanian hospitals.
2. To develop and validate a prediction model for ADR-related hospitalisation in patients aged ≥65 years.
3. To investigate the occurrence of repeat ADR-related admissions in elderly patients within 12 months of a hospital admission to a medical ward due to an ADR,
4. To investigate the utility of a validated ADR score in identifying patients at higher risk of a repeat ADR-related hospitalisation.
5. To compare the rates of ADR-related hospitalisations using different methods of detection.

1.3. Thesis outline

This thesis is composed of seven chapters, including five manuscripts. At the time of submission of this thesis, three of the five manuscripts have been published in peer-reviewed journals, and the last two are under review. A brief description of each chapter is provided below.

Chapter 1 outlines a general introduction and background information to the research project.

Chapter 2 is a narrative literature review outlining the importance of the topic and the rationale for the study approach. This review outlines the need for the current research and was published in the journal *Clinical Interventions in Aging* in 2016.

Chapter 3 presents the descriptive findings of a prospective cross-sectional study conducted in two Tasmanian hospitals, namely the Royal Hobart Hospital (RHH) and the Launceston General Hospital (LGH). The study evaluated the proportion, clinical characteristics, causality, severity, preventability and outcomes of ADR-related admissions in older patients admitted to these hospitals. The study's findings provide a clear picture of the current extent of the problem of ADR-related admissions in the elderly. The results were published in the journal *Drug Safety* in 2017.

Chapter 4 describes the development and validation of an ADR tool, named the "PADR-EC (Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients) score" to identify patients aged ≥65 years at risk of ADR-related

hospitalisation. The ADR tool was developed and validated using the prospective data from the RHH (the derivation cohort) and the LGH (the validation cohort) respectively. The results were published in the journal *PLoS ONE* in 2016.

Chapter 5 describes the findings of a retrospective study, which investigated the occurrence of repeat ADR-related hospital admissions in elderly patients within 12 months of an ADR-related admission to a medical ward. This study also investigated whether the PADR-EC score could be useful in identifying patients at higher risk of a repeat ADR-related hospitalisation. This study followed elderly participants who were hospitalised with an ADR from the PADR-EC study to identify repeat ADR-related hospital admissions within 12 months of discharge. The manuscript is under review in the journal *Drugs & Aging.*

Chapter 6 describes the findings of a retrospective study, which compared the rates of ADR-related hospitalisations using different methods of detection. This study linked the records of prospectively enrolled RHH patients from the PADR-EC study, where clinical pharmacists prospectively identified ADRs, to their hospital administrative data. The manuscript is under review in the journal *Pharmacoepidemiology and Drug Safety.*

Chapter 7 presents an overall discussion of the study findings, implications for practice and policy and recommendations for future research. This chapter ends with an overall conclusion.

CHAPTER ONE

1. Introduction

"The person who takes medicine must recover twice, once from the disease and once from the medicine."

-William Osler, M.D. (1849-1919).

1.1. Preface

Patient safety is defined as "the prevention of harm to patients" [11], and medications can be an important source of patient harm. The purpose of this chapter is to provide a general introduction to the research project. This chapter focusses on the ageing population, drug-related problems (DRPs), adverse drug reactions (ADRs), ADRs as a cause of hospital admissions, ADRs in the elderly, ADRs as a cause of hospital admissions in the elderly, repeat ADRs and different methods of ADR detection and various strategies used to prevent the risk of ADR-related admissions in elderly patients.

1.2. The ageing population

According to the World Health Organisation (WHO) report on ageing and health, the number of people aged 60 years or older will rise from 900 million to 2 billion between 2015 and 2050 (moving from 12% to 22% of the total global population) [12]. In Australia, the estimated population in 2016 was 24.4 million, of whom 3.7 million (15.2%) were aged 65 or older [13]. The number of elderly Australians is projected to increase more rapidly over the next decade as further cohorts of those born between the years 1946 and 1964 turn 65 [14]. These projections were estimated to be from 3.2 million

in 2012 to between 5.7 million and 5.8 million in 2031, and to between 9.0 million and 11.1 million in 2061 [15]. In 2009, about half (49%) of Australian people living in the community aged 65-74 had five or more long-term conditions or chronic diseases; this rate increased to 70% of those aged 85 or over [16]. In other international findings, the prevalence of multiple chronic conditions or multimorbidity [17] in older patients ranges from 55% to 98% [18]. The ageing population, together with a concomitant rise in the number of people living with multimorbidity, has major implications for both healthcare needs and higher healthcare costs associated with disability and functional decline or poor quality of life [18, 19]. In a cross sectional analysis conducted on a nationally random sample of older patients, the odds of experiencing a preventable inpatient admission were almost 99 (odds ratio [OR] 98.52 (95% CI 86.11-112.72) times higher among older people with four or more chronic conditions in comparison to their counterparts without a chronic condition [20]. The use of multiple medications and/or the administration of more medications than are clinically indicated [21], termed polypharmacy [22], is often associated with multimorbidity because patients receive and accumulate medications over time to treat each disease [23]. Polypharmacy is common among elderly Australians admitted to medical units of Australian hospitals [24]. Similar findings of polypharmacy were observed in a descriptive study in the United States (US), which found at least five or more prescription medications were used by 36% of community-dwelling older adults aged 62-85 years old [25].

1.3. Drug-related problems

The combination of an increasingly ageing population [15, 26], together with the growing use of multiple medications, leads to an increased risk for problems associated with

pharmacotherapy, collectively referred to as DRPs [27]. A DRP is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcome [28]. These DRPs, also termed 'medication incidents' [29], may adversely affect successful pharmacotherapy in a given patient. A medication incident can occur at any point in the medication use process (ordering, transcribing, dispensing, administering and monitoring) [30]. Medication incidents may include medication errors (MEs), adverse drug events (ADEs) and ADRs [31]. A ME error is defined as:

> Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems including prescribing, order communication, product labelling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use [32].

MEs are common, although relatively few result in ADEs [33], which are defined as injuries resulting from the use of a drug [34]. ADEs may also result from the manner in which the medicine is used (such as an error or system failure) [29]. MEs with potential for injury but in which no injury occurred have been classified as potential ADEs [33]. Some ADEs are termed ADRs, which result from the pharmacological actions of the medicine itself [29]. The WHO defines an ADR as "a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [36, 37]. Various authors have described the relationship between MEs, ADEs and ADRs. According to Bates et al. only a small proportion of MEs represent an ADE or a potential ADE [33]. Among these ADEs, only some ADEs are associated with a ME while others are not, which indicates that some ADEs would have been considered as ADRs according to the WHO definition [38]. However, all potential ADEs are MEs since they are

unintentional medication discrepancies which do not actually cause any injury, either because of specific circumstances, chance, or because the error is intercepted and corrected [30, 35]. Ackroyd-Stolarz et al. classified DRPs into those that result in injury and those that do not. The DRPs that result in injury include MEs, ADEs and ADRs whereas the non-injury DRPs include MEs and potential ADEs [39]. Nebeker et al. explained the relationship between key terms in DRPs, which is depicted in Figure 1 [40]. The grey areas represent injuries caused by drug use (ADEs). The dark grey area represents harm caused by a drug (ADRs). MEs are more common than ADEs, and less than 1% of MEs result in harm [33].

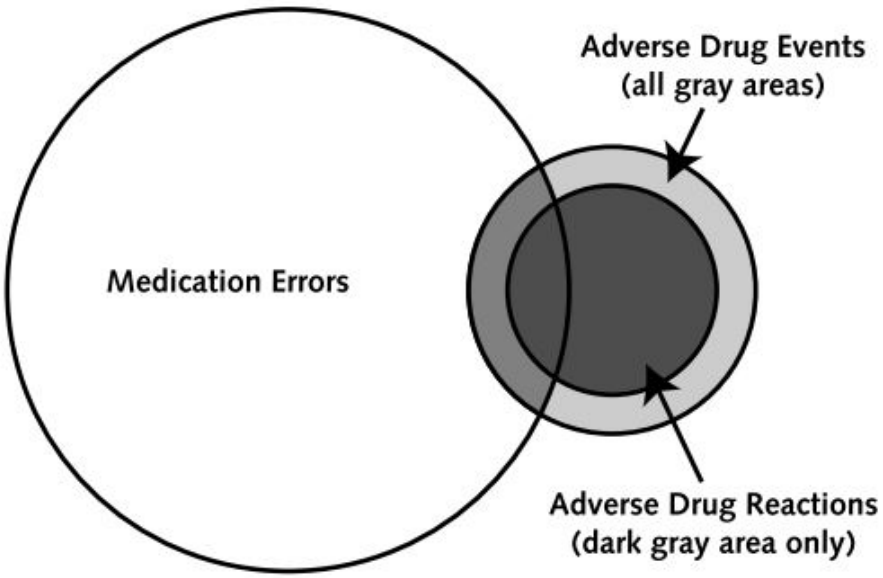

Figure 1. Relationship of key terms in drug-related problems

Reprinted with permission from Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 2004; 140:795-801[40].

1.4. Adverse drug reactions

ADRs are the most common DRPs [41-43]. ADRs are harms caused by drugs administered at usual therapeutic doses and are the primary focus of regulatory agencies and post-marketing surveillance [40]. The WHO defines an ADR as “a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function” [2, 37]. This definition excludes therapeutic failures, under-treatment, intentional and accidental poisoning (i.e., overdose) and drug abuse. The thalidomide tragedy in the 1960s has intensified the interest in ADRs worldwide [44]. ADRs were ranked the fourth to sixth leading cause of death in the US [36], and ADRs cause almost 197,000 deaths annually throughout the European Union [45]. Fatal ADRs account for approximately 3% of all deaths in the general population based on a Swedish study [46]. Another study estimated that over 350,000 ADRs occur each year in US nursing homes [34]. The Institute of Medicine reported that an estimated 7,000 deaths occur annually due to ADRs out of the total 44,000 to 98,000 deaths occur annually from medical errors [47] in the US. ADR prevalence is often reported in the literature as a proportion of hospital admissions, hospitalisations or ADRs occurring in outpatient settings. A retrospective observational study in Australia in 2004 concluded that 3.3% of hospitalisations were associated with an ADR that occurred as a cause of, or during admission [48]. Another study in general practice patients in Australia revealed a high frequency (10.4%) of ADEs in patients attending general practice, and for 95.3% of these patients, one reason for the most recent event was an ADR [49].

1.4.1. Adverse drug reactions as a cause of hospital admissions

ADRs can cause serious harm to patients and can lead to hospital admissions. ADRs as a reason for hospitalisation were first reported in Belfast hospitals in 1965-1966 [50, 51]. In Europe, the median percentage of hospital admissions due to an ADR was 3.5%, based on a recent systematic review of observational studies [52]. In another systematic review of prospective observational studies, the median prevalence of hospital admissions associated with ADRs was 6.3% [53]. In 2013-14, about 1% of all hospital separations (single patient encounters resulting in discharge [48]) in Australia were reported to have a drug-related principal diagnosis [54]. The most recent Australian data (2008-2013) shows that the proportion of all hospital admissions that are medication-related is between 2% and 3% [55], and approximately 50% of these are potentially preventable [29], causing an estimated annual cost of AUD $1.2 billion [55]. A 2012 meta-analysis also reported that more than 50% of ADRs causing emergency visits or hospital admissions are potentially preventable [56]. A 10-week study on drug-related admissions to an Australian hospital estimated that almost 10% of medical admissions to the hospital were drug-related and most of these admissions were attributable to an ADR (30.9%) or intentional overdose (38.2%) [57]. In other international studies, the prevalence of ADR-related admissions has ranged from 1.7% to 8.4% [58-61].

1.4.2. Adverse drug reactions in the elderly

ADRs occur commonly in the elderly. Premarketing drug clinical trials often exclude elderly patients, even though they are the major users of medications [62]. Hence, there is a lack of sufficient clinical data in the elderly on the risk-benefit ratio of medications. There is often a need for dosage adjustments from initially approved doses in elderly

patients, which illustrates the lack of adequate clinical data in this patient group [62]. Older patients are particularly susceptible to ADRs since ageing is associated with pharmacokinetic and pharmacodynamics changes that might affect drug concentration and effects [63]. There is a natural decrease in creatinine clearance with true renal ageing in addition to other specific diseases or medications, which might change glomerular filtration rate in the elderly [64]. Additionally, a decline in the ability of the liver to inactivate toxins may contribute to a pro-inflammatory state, which in turn downregulates drug metabolism and results in reduced systemic clearance of prescribed medications leading to ADRs in the elderly [65]. The adverse effects of some drug combinations may be synergistic and be greater than the sum of the risks of adverse effects of either drug used alone [66]. Thus, the risk for ADRs increases with advancing age though the clinical reality is far more complex [67]. In one study, the risk of ADR-related deaths was greatest in older adults aged 75 years or older (OR 6.96, 95% CI 6.30–7.69) [68].

1.4.3. Adverse drug reactions as a cause of hospitalisation in the elderly

ADRs are frequently a cause of hospitalisation or may happen during hospital admission [51]. Of concern are ADR-related hospital admissions, particularly in the elderly who are the most likely to develop ADRs as they receive most medications [6]. ADRs have been found to be the most common type of drug-related admission in the elderly [69]. A survey of drug-related admissions in older medical patients in Canada estimated 19% of the admissions were drug-related, and a frequent contributing cause was ADRs (48%) [43]. A recent meta-analysis found one in ten hospital admissions in older patients were due to ADRs [6]. A retrospective cohort study (2004-2008) amongst elderly Australian veterans estimated that the overall proportion of potentially preventable medication-related hospitalisations was 20.3% [70]. When these results are extrapolated to the overall

Australian population aged ≥65 years, as many as 90,000 admissions annually are potentially preventable medication-related admissions. In Australia, the age-standardised rate of ADR-related hospital stays increased from 2.5 per 1000 person-years in 1981 to 12.9 per 1000 person-years in 2002 [5]. A detailed discussion of ADRs as a reason of hospitalisation in the elderly, including the risk factors, is provided in Chapter 2.

1.4.4. Repeat adverse drug reactions-related hospitalisation in the elderly

ADRs that result in hospitalisation in patients with a history of ADR-related hospitalisation, or 'repeat ADRs,' are increasingly common and are of equally significant concern as ADRs though few studies have examined repeat ADRs in the elderly. In a Hong Kong-based study, ADRs were found to be one of the significant risk factors (OR 4.19, 95% CI 1.56–11.2) for early emergency readmission in elderly medical patients [71]. In a US study on the association between post-discharge ADRs and 30-day hospital readmissions in patients aged 80 and older, 23.4% of all readmitted patients had an ADR that contributed to readmission [72]. A population-based longitudinal study in Australia estimated that repeat ADR-related hospitalisations consistently increased faster than first-time ADRs in the elderly in Western Australia from 1980 and had reached 30.3% of all ADRs by 2003 [73]. In another study in Australia, comorbidity, but not advancing age, predicted repeat admission for ADRs in the elderly, especially those with comorbidities often managed in the community [8].

1.4.5. Detection of adverse drug reactions

Several methods exist for the detection of ADRs. These are spontaneous reporting of ADRs, utilising administrative databases, computerised surveillance of ADRs, manual

chart reviews and prospective and intensive monitoring. These methods are discussed below.

1.4.5.1. Spontaneous reporting

In spontaneous reporting, healthcare professionals report ADRs whenever there is suspicion of ADRs. Using this system, case reports of ADRs are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority [74]. The main drawback of this method is underreporting of ADRs [75], and this method identifies the lowest number of ADRs compared to other methods of ADR detection [76]. It also tends to result in more reports related to newer 'drugs of interest' rather than established therapies [77].

1.4.5.2. Administrative databases

Administrative databases, electronic health records, and disease registries contain a large amount of health data that can be used to identify health outcomes in clinical practice [78]. Administrative databases increasingly use the International Classification of Diseases (ICD) 10^{th} Revision system for identifying drug-related hospital admissions, readmissions or ADRs by assigning codes to inpatient discharges [79-81]. In Australia, the Australian Modification of ICD-10 (ICD-10-AM) is used, which allows ADR codes to be applied to any diagnosis and thereby retrospective ADR reporting is possible [48].

1.4.5.3. Computerised surveillance

In some studies, the use of computer-assisted screening of laboratory values that are potentially associated with ADRs were utilised to identify ADRs [82, 83]. Computer-

assisted surveillance identifies many ADRs not identified by spontaneous reporting but detects less ADRs compared to chart review [76]. However, few hospitals are equipped with these types of systems. For example, LDS Hospital, Salt Lake City, Utah (USA) has an integrated computerised surveillance system that prospectively screens electronic patient data for indicators of ADRs [84].

1.4.5.4. Manual chart or medical record review

In some studies, ADRs are detected either prospectively or retrospectively by reviewing patient charts, generally by specialists in ADR identification [85]. ADR identification using chart reviews identifies more ADRs than spontaneous reporting, but it is expensive and time-consuming [76].

1.4.5.5. Prospective and intensive monitoring

Prospective and intensive monitoring refers to studies performed prospectively in hospitalised patients by skilled staff (doctors, nurses or pharmacists), often involving interviews with patients or health team members [85]. In this method, a population of patients receiving an individual drug, alone or in combination with other drugs, is kept under close surveillance; this method, though very expensive, results in an increased rate of ADR reporting compared to other methods of ADR detection [37].

1.5. Prevalence of ADR-related admissions in the elderly based on methods of detection

The different methods of ADR detection result in different rates of reported ADRs [51]. In a systematic review of prospective observational studies, the estimated median

prevalence of hospital admissions associated with ADRs in the elderly was 10.7% (interquartile range, 9.6%–13.3%) [53]. In this review, studies that utilised multiple ADR identification methods such as medical record review and patient interview reported higher ADR admission rates (9.6%–15.7%) compared with studies that used medical record review alone (7.2%–10.6%). In another recent systematic review of hospital-based observational studies (prospective and retrospective), the median prevalence of ADRs leading to hospitalisation in the elderly in the acute care setting was 10.0% (95% CI, 7.2%–12.8%) [86]. The prevalence of ADR-related admissions based on the different method of detection in the elderly population admitted to the medical wards is shown in Table 1.

Table 1. Prevalence of ADR-related admissions based on different methods of detection in the elderly admitted to medical wards

Method of ADR detection	ADR prevalence	Location	Author/year
Prospective and intensive monitoring	14.6%	Greece	Alexopoulou et al., 2008 [87]
	13.3%	Australia	Chan et al., 2001 [88]
	10.79%	UK	Kongkaew et al., 2013 [89]
	11.29%	Brazil	Passarelli et al., 2005 [90]
	19.48%	Brazil	Varallo et al., 2011 [91]
Spontaneous reporting	3.6%	Belgium	Somers et al., 2007 [92]
Medical record review (prospective)	2.9%	UK	Rogers et al., 2009 [93]
	4.6%	Italy	Caamano et al., 2005 [94]
	10.66%	Canada	Courtman et al., 1995[95]
Medical record review (retrospective)	7.8%	Slovakia	Wawruch et al., 2009 [96]
Clinical coding	2.9%	Netherlands	van der Hooft et al., 2006 [97]

Abbreviations: ADR, adverse drug reaction; UK, United Kingdom.

There are also studies that compared the prevalence of ADR-related admissions using different methods of detection in the same cohort, though there is a scarcity of such studies in the elderly. In a study conducted in Slovenia, the frequency of ADRs-related admissions identified using retrospective medical review was much higher (5.8% of admissions) than that identified by the ICD-10 coding system (0.2%) [98]. In this study, no ADRs were identified using the spontaneous reporting method. In another study in the Netherlands, 1.8% of all acute hospital admissions were ADR-related identified by ICD-10 coding, and only 1% of these coded ADRs was identified using the spontaneous ADR

reporting system [97]. In a United Kingdom (UK) based study, only 31.5% of the ADR-related admissions identified using a prospective observational method in a paediatric centre were also detected using ICD-10 codes [99], while in a study conducted in two Canadian hospital emergency departments (EDs), only 28.1% of prospectively identified ADEs (62 of 221 events) were identified using ICD-10 codes [100].

1.6. Strategies for preventing adverse drug reaction-related hospitalisations in the elderly

Prevention of unnecessary hospitalisations by ADRs is an important goal in health policy decision-making [101]. Several strategies have been described in the literature and are discussed below.

1.6.1. Medication review

'Medication review is a structured evaluation of patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting DRPs and recommending interventions' [102]. In 2008, the National Prescribing Centre, Department of Health, UK defined three types of medication review depending on the purpose of the review [103, 104]. The classification includes:

i) Prescription review (Type 1): This addresses technical issues relating to a prescription, and takes place in the absence of the patient.

ii) Concordance and compliance review (Type 2): This addresses issues relating to the patient's medicine-taking behaviour, and takes place usually in the presence of the patient.

iii) Clinical medication review (Type 3): This addresses issues relating to the patient's use of medicines in the context of their clinical condition, and takes place in the presence of the patient.

There is a range of potential approaches to medication review used in different countries. In the UK, US, and Australia, clinical medication review is increasingly used [27]. In the UK, community pharmacists in England and Wales provide Medicines Use Reviews (MURs) which are now targeted towards particular patient groups, including those taking high-risk medicines [105]. Dispensing practices in England provide Dispensing Review of Use of Medicines (DRUM), and its main aim is to help patients understand their treatment and to identify potential DRPs [104]. In Scotland, the Chronic Medication Service (CMS) is another similar service in community pharmacies, aimed at patients with long-term conditions [106]. In the US, Medication Therapy Management (MTM) services are provided by community pharmacists and other service providers, with the aim of improving adherence or detecting ADEs and medication misuse [107]. Furthermore, in the US, patients are asked to bring all their medications including over-the-counter and alternative medicines to a community pharmacist for a detailed medication review ('brown bag reviews') [108]. In Australia, accredited pharmacists conduct medication reviews for patients to identify and resolve DRPs [109]. The two established pharmacist-led medication review programs are Home Medicines Review (HMR) and Residential Medication Management Review (RMMR) [110]. HMR or Domiciliary Medication Management Review (DMMR) is a collaborative medication review for people in the community, and RMMR is for residents of aged care facilities [111]. In both programs, the main goal is to maximise an individual patient's benefit from

their medication regimen and prevent or address medication-related problems through a team approach involving the general practitioner (GP) and a pharmacist. The Australian Department of Health also commenced two new programs in the last five years, Medicines Use Review and the Diabetes Medication Management Services, now known as the MedsCheck and Diabetes MedsCheck programs, respectively [112]. The MedsCheck/Diabetes MedsCheck Program involves in-pharmacy reviews with patients who are taking multiple medications and/or have newly diagnosed or poorly controlled type 2 diabetes. These reviews are aimed at enhancing the quality use of medicines and reducing the number of ADEs experienced by patients.

Studies on the effectiveness of medication reviews

Several studies have investigated the effectiveness of medication reviews. While most have demonstrated that medication reviews are effective in terms of DRP identification and rationalisation of medication regimens, the results relating to health outcomes have been more variable. In South East London, a study of brown bag reviews by pharmacists resulted in pharmacist intervention in 87% of medication reviews and identified 12% of reviews with medication-related problems such as ADRs that could potentially result in a hospital admission [113]. In a further 34% of cases, the potential for an improved outcome for the patient if drug therapy was changed was also identified. The implementation of clinical medical reviews in Dutch community pharmacies identified an average of 2.9 DRPs per review [114]. In the Netherlands, pharmacist-based medication reviews in the elderly significantly reduced the mean number of DRPs per patient (mean difference -16.3%, 95% CI 24.3–8.3) [115]. In a randomised controlled trial in elderly primary care patients, a pharmacist-led structured medication review

contributed to reductions in numbers of drugs and maintenance of self-rated health in elderly patients with polypharmacy [116]. However, in a cluster randomised controlled trial, clinical medication reviews did not influence the quality of life and geriatric problems in the elderly, and the higher percentage of resolved DRPs in the intervention group did not result in effects on the patients' health [117]. In another randomised controlled trial in the UK, home-based medication review was associated with a significantly higher rate of hospital admissions in the elderly and did not significantly improve the quality of life or reduce deaths [118]. A randomised controlled study, which evaluated pharmacist-conducted follow-up at home of high-risk elderly patients discharged from an Australian hospital, found that 45% of the control group patients had unplanned readmissions to the hospital during the 90 days following discharge, compared to 28% of the intervention group patients ($P = 0.05$) [119]. In another randomised controlled trial in older adults undergoing first-time transfer from three Australian hospitals to a long-term care facility, the addition of a pharmacist transition coordinator improved aspects of the inappropriate use of medicines across health sectors, but not ADEs [120]. A pilot study in Australia concluded that an HMRs conducted post-discharge could identify clinically significant medication-related issues [121]. In a prospective, non-randomised controlled cohort study in Australia, the patients who received a post-discharge service that involved point-of-care international normalised ratio monitoring, warfarin education and an HMR demonstrated statistically significantly decreased rates of combined major and minor haemorrhagic events [122]. In this study, combined haemorrhagic and thrombotic events were also decreased, while persistence with warfarin therapy improved. In a retrospective study of DRPs in Australian aged care homes, medication reviews by clinical pharmacists identified potential DRPs with a risk

of ADR in 96% of the residents [123]. In another retrospective cohort study in Australian war veterans, GP-pharmacist collaborative medication reviews delayed the time to next hospitalisation for bleeding in those treated with warfarin during the period 2 to 6 months after the review, but this was not sustained over time [124].

Systematic reviews on the effectiveness of medication review

Many systematic reviews have been published addressing the effectiveness of medication review though few have focussed on community settings. A recent overview of systematic reviews of pharmacist-led medication reviews in community settings supports the value of medication reviews by pharmacists for a range of clinical outcomes such as diabetes control (78% of studies reporting the outcome), blood pressure control (74%), cholesterol (63%), medication adherence (56%) and medication management (47%) [125]. Medication review as an isolated short-term intervention, irrespective of the patient population and the outcome measures used, influenced most drug-related outcomes, with minimal effect on clinical outcomes and no effect on quality of life [126].

Currently, there is less evidence on the effectiveness of medication reviews on outcomes related to adverse events in the elderly population. In a review addressing the outcomes reported in trials of medication review in older patients, only 21% of the studies evaluated the impact of medication reviews on adverse events (AEs) such as ADRs or drug-related hospital admissions and consequently, only four published studies (9%) had a primary outcome in the AE domain [127]. Most of the outcomes were related to medication use (the number of drugs, the number of potentially inappropriate medicines [PIMs], or overuse) (n = 114, 35%) and healthcare use (hospitalisations or GP visits) (n = 74, 23%). Another systematic review addressing the processes and outcomes of

clinical medication review in community settings in Australia concluded that clinical medication reviews are beneficial in improving the quality use of medications. However, the impact on clinical outcomes is inconclusive [128].

In conclusion, clinical medication review appears to be a useful strategy for preventing ADRs among the different types of medication reviews. However, there is not sufficient evidence to determine which level of medication review is most effective in preventing ADR-related hospitalisations in the older population.

1.6.2. Medication reconciliation

Medication reconciliation is a formal process of obtaining and verifying a complete and accurate list of each patient's current medicines, matching the medicines the patient should be prescribed to those they are actually prescribed [129]. It identifies and resolves unintentional discrepancies between patients' medication lists across transitions in care [130]. In systematic reviews, pharmacy-led medication reconciliation interventions were found to be an effective strategy in reducing medication discrepancies [131]. A prospective, randomised, non-blinded study, assessing the effectiveness and feasibility of pharmacist-led admission medication reconciliation for geriatric patients, identified a significant number of discrepancies, including predominantly omissions and wrong doses, dosage forms, or frequencies [132]. Most unintentional discrepancies identified had no clinical significance and did not reduce post-discharge hospital utilisation, or the impact of medication reconciliation on clinical outcomes such as reductions in hospital readmissions was less clear [130, 133]. In a systematic review, hospital-based medication reconciliation interventions did not have any effect on clinical outcomes, though the medication reconciliation was focussed on patients at high risk of

adverse events [134]. In a prospective, randomised, single-period longitudinal study, pharmacist involvement in hospital discharge transitions of care of high-risk patients through medication reconciliation, medication education, and post-discharge call-backs had a positive impact on decreasing composite inpatient readmissions and ED visits [135]. In this study, there was no significant difference in ADEs observed between the intervention group and the control group. A recent systematic review showed that pharmacist-led medication reconciliation at hospital transitions in adult patients substantially reduced ADE-related hospital revisits (relative risk reduction of 67%), ED visits (28%) and hospital readmissions (19%) [136].

Medication reconciliation, in addition with other services, prevented ADR-related hospital admissions in two studies. In a prospective controlled study, medication reconciliation upon admission and discharge, and medication review and monitoring significantly reduced unscheduled drug-related hospital revisits ($p = 0.0469$) among elderly patients [137]. In a randomised trial, a pharmacist intervention focused on medication reconciliation, medication review, patient counseling, and telephone follow-up was associated with a lower rate of preventable ADEs 30 days after hospital discharge [138]. In this study, discharge medication regimens were compared with pre-admission regimens, all discrepancies were reconciled, and patients were screened for previous DRPs. Additionally, in order to explore any discrepancies, the pharmacist compared the patient's self-reported medication list with the discharge list during the follow-up telephone call.

1.6.3. Avoiding inappropriate medications

Inappropriate prescribing in the elderly has become an important public health issue worldwide since the prescription of PIMs is associated with an increase in AEs, prescribing cascades, morbidity, mortality and health-care costs [139, 140]. Prescribing appropriateness can be evaluated by process or outcome measures that are explicit (criterion-based) or implicit (judgement-based) [141]. Explicit criteria tend to focus on specific medications or disease states and are usually developed from published reviews, expert opinions, and consensus techniques [140, 142]. Implicit criteria are not drug or disease specific and rely on clinical judgement or expert professional judgement but are more patient-focused [141, 142].

Various explicit criteria have been developed by experts in the US [143] and Canada [144] to identify PIM use in elderly patients, to help minimise DRPs. The most widely used criteria is the one developed by Beers and colleagues for PIM use in older adults, which was published in 1991 [143]. The original Beers criteria have been revised and updated in 1997, 2003, 2012 and 2015 [145-148]. In 2015 update by the American Geriatrics Society, 50 medications or medication classes are divided into three categories, namely PIMs that should be (i) avoided in older adults, (ii) avoided in older adults with certain diseases and syndromes and (iii) used with caution [148]. The new additions in the updated version are selected drugs for which dose adjustment is required based on renal impairment, and the addition of selected drug-drug interactions. In 2008, the Screening Tool of Older Person's Prescriptions (STOPP) criteria was developed for identifying inappropriate prescribing in the elderly [149]. The START (Screening Tool to Alert doctors to the Right Treatment) criteria, another screening tool was developed and validated in 2007 to detect prescribing omissions in elderly patients [150].

STOPP/START is a comprehensive screening tool that enables the prescribing physician to appraise older patients' prescription drugs in the context of their current diagnoses [151, 152]. In a prospective study in the elderly, STOPP criteria PIMs were significantly associated with avoidable ADEs in older people that cause or contribute to urgent hospitalisation [153].

The most cited implicit criteria is the Medication Appropriateness Index, which was developed by Hanlon et al. in 1992 [141, 154]. This tool assesses prescribing appropriateness using ten criteria: indication for the drug, effectiveness for the condition, correct dose, correct direction, practical directions, clinically significant drug-drug interactions, clinically significant drug-disease interactions, unnecessary duplication, acceptable duration of therapy and cost effectiveness [154]. The Assessment of Underutilisation of Medication is another tool, which assessed omitted but necessary drug therapies for chronic conditions [155, 156]. The Inappropriate Medication Use and Prescribing Indicators Tool is an instrument developed by Australian researchers in 2008, and is based on 45 explicit and three implicit prescribing indicators [157].

1.6.4. Computer-assisted decision support systems

Computerised physician order entry (CPOE) and clinical decision support systems (CDSSs) have the potential to improve drug safety [158]. CDSSs and CPOE provide support in the ordering stage of the medication use process by identifying PIMs, drug interactions, ADRs, appropriate drug dosage and contraindicated treatments [3, 159]. They also use different algorithms and tools to identify drug-related illness. In one study, the implementation of CPOE reduced the potential ADE rate by 84% [160]. However, in

a systematic review, CDSSs inconsistently improved process of care measures and did not improve patient outcomes [161].

1.6.5. Comprehensive geriatric assessment

Comprehensive geriatric assessment allows a complete and global assessment [3] and is used to determine the medical, psychosocial, functional capabilities of a frail older adult to develop a coordinated and integrated plan for treatment and long-term follow-up [162]. A comprehensive assessment and management of healthcare problems in the elderly help in recognising and preventing potential DRPs and thereby reduces the risk of ADRs [163]. In a randomised controlled trial, outpatient geriatric evaluation and management reduced serious ADRs and reduced suboptimal prescribing in frail elderly patients compared with usual care [164].

1.7. Adverse drug reaction risk prediction tools

ADR risk prediction tools for use in the elderly have been developed in recent years [9, 10]. ADR risk stratification in the elderly could assist in case prioritisation and allow more cost-effective allocation of additional health resources towards this group to reduce their risk of developing ADRs. However, the available ADR prediction tools developed for use in the elderly are used to identify ADRs occurring in hospital, and no tools have been developed to date to predict ADR-related admissions in older patients living in the community. The development of a validated tool to identify elderly patients at risk of ADR-related admissions requires urgent action since this approach has never been adopted before in the field of ADRs. The need for the development of such a tool is discussed in detail in Chapter 2.

CHAPTER TWO

2. Hospitalisation in Older Patients due to Adverse Drug Reactions – the Need for a Prediction Tool

2.1. Preface

The previous chapter provided an overview of the evidence relating to adverse drug reactions (ADRs) and highlighted various strategies to prevent ADR-related hospitalisation in the elderly. The review identified several gaps in the literature, including the lack of a narrative review investigating the need for a prediction tool for ADR-related hospitalisation in older patients. Hence, this chapter presents a narrative evaluation of studies that evaluated the predictors of ADR-related hospitalisation in the elderly and recommends the need for a prediction tool.

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2.2. Abstract

Adverse drug reactions (ADRs) represent a major burden on society, resulting in significant morbidity, mortality and healthcare costs. Older patients living in the community are particularly susceptible to ADRs and are at an increased risk of ADR-related hospitalisation. This review summarises the available evidence on ADR-related hospital admission in older patients living in the community, with a particular focus on risk factors for ADRs leading to hospital admission and the need for a prediction tool for risk of ADR-related hospitalisation in these individuals. The reported proportion of hospital admissions due to ADRs has ranged from 6% to 12% of all admissions in older patients. The main risk factors or predictors for ADR-related admissions were advanced age, polypharmacy, comorbidity and potentially inappropriate medications. There is a clear need to design intervention strategies to prevent ADR-related hospitalisation in older patients. To ensure the cost-effectiveness of such strategies, it would be necessary to target them to those older individuals who are at highest risk of ADR-related hospitalisation. Currently, there are no validated tools to assess the risk of ADRs in primary care. There is a clear need to investigate the utility of tools to identify high-risk patients to target appropriate interventions toward prevention of ADR-related hospital admissions.

Keywords: adverse drug reactions, hospital admission, prediction, older patients, primary care, risk factors

2.3. Introduction

Medication-related adverse events (AEs) in general practice represent an important cause of morbidity and are thought to cause between 10% and 30% of all hospital admissions in older patients [165, 166]. These AEs are defined as “any untoward medical occurrences that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment” [40]. Among these AEs, adverse drug reactions (ADRs) represent a major burden, causing significant morbidity, mortality, and health care costs [3, 4]. The World Health Organisation (WHO) defines an ADR as any noxious, unintended, and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning, and drug abuse [37, 167]. ADRs can be assessed as severe, moderate, or mild reactions [88]. A severe ADR is life-threatening, causing permanent damage or requiring intensive care. Moderate ADRs require hospital admission, a change in therapy, or specific treatment. In a meta-analysis of prospective studies, 100,000 deaths per year could be attributed to ADRs in the USA, which highlights the seriousness and extent of the problem [36]. Furthermore, a Swedish study estimated that 3.1% of deaths in the general population (including subjects who died in and outside hospitals) were attributed to ADRs [46].

Older patients are particularly susceptible to ADRs due to multiple comorbidities, cognitive and functional impairment, a high prevalence of multiple medications (polypharmacy), [168] and age-related changes in pharmacokinetics and pharmacodynamics [4]. A significant consequence of ADRs in older adults living in the community is hospitalisation and its related costs [169]. These patients then become susceptible to hospitalisation-related complications, such as cardiovascular and neurological disorders, nosocomial infections, and deconditioning [170]. It may be

challenging for primary care physicians (or general practitioners [GPs]) to easily identify patients who are at risk of hospitalisation due to ADRs, partly due to significant time pressures in office-based practice [171]. This narrative review explores our current understanding of ADR-related hospitalisation in older patients, with a particular focus on risk factors and the need for a prediction tool for ADR-related hospitalisation for utilisation in community settings.

2.4. ADR-related hospitalisation in older patients – how significant is the problem?

Based on a retrospective cohort study in a veteran population (median age 81 years), the overall proportion of potentially preventable medication-related hospitalisations was 20.3% over a 5-year period [70]. ADRs were the most common cause, accounting for one-third of hospitalisations based on a study by Chan et al. [88]. Data collected from GP encounters in 2003–2004 in Australia indicated that ADRs represented the most common adverse drug event (ADE) in the community (72%), of which the majority were moderate or severe and required hospitalisation [49]. The proportion of all hospital admissions due to ADRs has ranged from 6% to 12% among older patients [96, 169, 172-174]. Also, one study conducted in Canada found that emergency department visits and hospital admissions due to ADRs in older patients cost an estimated US$35.7 million annually [175].

2.5. Severity, causality, and avoidability of ADR-related hospitalisation in older patients

ADR-related hospitalisation can lead to fatal outcomes and increased length of stay in older patients [58, 176]. The severity of ADR-related admissions was assessed in a

prospective study, in which 18.6% of cases were identified as severe ADRs [87]. The most severe ADRs were related to haemorrhage and other haematological disorders, and acute renal failure. Most of the ADRs causing hospital admission in older patients were type A reactions, which are predictable from the known pharmacology of the drug, [58, 176] whereas type B reactions (bizarre or non-dose-related reactions) accounted for only 8.1% based on a cross-sectional study [176].

Since ADRs are a major cause of morbidity and mortality, it is important to demonstrate a causal relationship between the drug and the adverse clinical event. Furthermore, it is often difficult to decide if an adverse clinical event is an ADR or due to deterioration in the patient's disease state. Therefore, causality assessment is used to determine the likelihood that a drug caused a suspected ADR [177]. The most widely used and generally accepted causality assessment scales in clinical practice are the probability scales developed by the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, Sweden) and the Naranjo ADR Probability Scale [178, 179]. These scales use inter-rater agreement scores, which are superior to subjective clinical judgment. However, they can be difficult to interpret in the context of older patients with multiple comorbidities and medications [180]. Based on different studies, the majority of ADRs in older adults leading to hospital admissions were either probable or possible based on causality assessments [58, 87, 181]. Definite or certain ADRs accounted for only 4% and 6.8%, respectively, in some studies [173, 181].

While some ADR-related hospitalisations are unavoidable, even with the most extraordinary precautions (e.g., immunological reactions), more than half of hospital admissions for ADRs are preventable [88]. Potentially avoidable ADRs leading to hospital admission in older adults could be due to improper dosage, missed

contraindications and drug interactions, or re-exposure of patients who had known drug allergies. ADRs can be classified into definitely avoidable, possibly avoidable, unavoidable, and unclassifiable based on the Halls criteria [182]. Among the ADRs causing hospital admission in older patients, most were either definitely or possibly avoidable, with only 18.6%–28% of cases considered unavoidable [58, 173].

2.6. Most common ADRs causing hospitalisation in older patients

Advancing age can contribute to a significant increase in sensitivity to particular drugs and a corresponding increase in the incidence of ADRs [183]. Older patients demonstrate an exaggerated response to central nervous system-active drugs (e.g., benzodiazepines, anaesthetics, opioids) and a decreased response to some cardiovascular agents (e.g., beta-adrenergic agents) [184]. Also, the most important pharmacokinetic changes in older people include a decrease in the excretory capacity of the kidney, rather than a decline in the rate of hepatic drug metabolism [185]. The most frequent ADRs causing hospital admission in older patients are typically gastrointestinal disorders [4, 58, 87, 173, 176] and cardiovascular and metabolic/endocrine complications [4, 58, 87, 96, 169, 173]. A summary of the most common ADRs causing hospitalisation in older patients is shown in Table 2.

Table 2. Most common ADRs causing hospitalisation in the elderly

Most common ADRs	Examples
Gastrointestinal complications [4, 58, 87, 173, 176]	Gastrointestinal bleeding, peptic ulcer, erosive gastritis, nausea, vomiting
Cardiovascular disorders [58, 96, 169, 173]	Hypotension, bradycardia, falls, arrhythmias
Metabolic/endocrine complications [4, 87, 169]	Hypoglycaemia
Renal and urinary disorders [58, 87, 176]	Renal impairment, acute renal failure
Electrolyte disorders [58, 174]	Hypokalaemia, hyperkalaemia, hyponatremia
Nervous system disorders [169, 176]	Depressed level of consciousness, mental status changes

Abbreviation: ADRs, adverse drug reactions.

2.7. Drugs most frequently causing ADR-related hospitalisation in older patients

Older patients, due to the presence of multiple disease states, frequently use medications including prescription, over-the-counter, and herbal preparations. According to a survey conducted in 3,005 community-dwelling older adults aged 57–85 years in the USA, at least one prescription medication was used by 81% of the overall survey population, and five or more prescription medications were used by 36% of people aged 75–85 years [186]. The drugs most frequently causing ADR-related hospital admissions in older patients have varied between studies; these findings are summarised in Table 3.

Table 3. Most common drugs causing ADR-related hospital admission in the elderly

Most common drugs	Reference
Antibacterials	[4, 173, 174]
Anticonvulsants	[187]
Antineoplastic agents	[4, 188]
Antipsychotics	[4, 188]
Antithrombotics (anticoagulants and antiplatelets)	[87, 173, 174, 176, 187, 188]
Cardiovascular drugs	
Diuretics	[4, 58, 87, 174, 176, 188]
Cardiac glycosides	[4, 173, 187]
Angiotensin converting enzyme inhibitors	[87, 173, 176, 181, 187]
β-Blockers	[181, 187]
Antiarrhythmics	[87, 173]
Calcium channel blockers	[4]
Corticosteroids	[4]
Hypoglycaemics	[187, 188]
Nonsteroidal anti-inflammatory drugs	[4, 58, 87, 173, 176, 187]

Abbreviation: ADR, adverse drug reaction.

2.8. Predictors of and risk factors for ADR-related hospitalisation in older patients

Despite concerns that ADRs represent an important medical problem in older patients, the predictive factors are still poorly understood, particularly in the community-dwelling elderly. The characteristics and major findings of studies that have investigated the risk factors for ADR-related hospital admission in older patients are shown in Table 4.

Table 4. Studies investigating risk factors for ADR-related hospital admission in older patients

Study	Country and year conducted	Design	Duration	Settings	Mean/ median age (Years)	Main outcome measures	Predictors/risk factors
Onder et al. [4]	Italy 1988–1997	Multicentre pharmacoepidemiology survey	10 years	Academic hospitals	70	ADR severity, potentially responsible drugs, predictors	Female sex (OR 1.30, 95% CI 1.10–1.54) Alcohol use (OR 1.39, 95% CI 1.20–1.60) Number of drugs (OR 1.24, 95% CI 1.20–1.27 for each drug increase) Severe ADRs Age (OR 1.50, 95% CI 1.01–2.23 for age 65–79 years and OR 1.53, 95% CI 1.00–2.33 for age ≥80 years) Comorbidity (OR 1.12, 95% CI 1.05–1.20 for each point in the CCI) Number of drugs (OR 1.18, 95% CI 1.11–1.25 for each drug increase)
Marcum et al. [169]	US 2004–2006	Retrospective cohort	3 years	All admissions (veterans)	76.4	ADR causality, preventability, predictors	Polypharmacy (≥9 and 5–8 medications) (AOR 3.90, 95% CI 1.43–10.61 and AOR 2.85, 95% CI 1.0–7.85, respectively)
Mannesse et al. [172]	Netherlands 1994	Observational cross-sectional	3 months	University hospital	78	Risk indicators for severe ADRs	Fall before admission (OR 51.3, P=0.006) Gastrointestinal bleeding or haematuria (OR 19.8, P<0.001) Use of three or more drugs (OR 9.8, P=0.04)

Study	Country and year conducted	Design	Duration	Settings	Mean/ median age (Years)	Main outcome measures	Predictors/risk factors
Franceschi et al. [173]	Italy 2004–2005	Prospective cross-sectional	1 year	Geriatric	76.5	ADR prevalence, avoidability	Drug–drug interactions (32.3%) Inappropriate prescription (21.8%)
Wawruch et al. [96]	Slovakia 2003–2005	Retrospective cross-sectional	1.4 years	Internal medicine	76.6	ADR predictors	Ischaemic heart disease (OR 4.50, 95% CI 1.36–14.88) Depression (OR 2.49, 95% CI 1.08–5.77) Heart failure (OR 2.08, 95% CI 1.13–3.81)
Wu et al. [175]	Canada 2003–2008	Retrospective cohort	5 years	Emergency department	77	Incidence, cost, risk factors	Sex (for females, AOR 0.81, 95% CI 0.72–0.92) Age (AOR 1.03, 95% CI 1.02–1.04) CCI score >3 (AOR 1.86, 95% CI 1.48–2.33) Number of drugs (AOR 1.48, 95% CI 1.13–1.93 for 6–10 drugs and AOR 1.93, 95% CI 1.49–2.51 for >11 drugs) Multiple pharmacies (AOR 1.13, 95% CI 1.00–1.27) Newly prescribed drugs (AOR 1.17, 95% CI 0.93–1.47) Recent hospital admission (AOR 1.47, 95% CI 1.23–1.76) Long-term care residence (AOR 2.08, 95% CI 1.62–2.67)
Pedros et al. [176]	Spain 2009–2010	Cross-sectional	120 days	Teaching hospital	75	ADR predictors	Age ≥65 years (OR 1.59, 95% CI 1.10–2.29) Number of drugs taken 3–5 (OR 5.07, 95% CI 2.71–9.50),

Study	Country and year conducted	Design	Duration	Settings	Mean/ median age (Years)	Main outcome measures	Predictors/risk factors
							6–9 (OR 5.90, 95% CI 3.16–11.01), and ≥10 (OR 8.94, 95% CI 4.73–16.89)
Alexopoulou et al. [87]	Greece 2005	Prospective cross-sectional	6 months	University hospital	65	Frequency of ADRs, causality, severity, preventability, predictors	Number of drugs (OR 1.064, 95% CI 1.019–1.109)
Olivier et al. [188]	France 2002–2003	Prospective cross-sectional	4 weeks	Emergency department	80.2	ADR incidence, risk factors	Number of drugs (OR 1.18, 95% CI 1.08–1.29) Self-medication (OR 2.34, 95% CI 1.18–4.66) Use of antithrombotics (OR 2.26, 95% CI 1.33–3.88) Use of antibacterial drugs (OR 4.04, 95% CI 1.50–10.83)
Malhotra et al. [189]	India 2000	Prospective cross-sectional	7 months	Emergency department	72.5	Risk factors	Number of drugs ≥3 (OR 4.3) Consulting >3 physicians (OR 5.7) Living alone (OR 4.3)
Chen et al. [190]	Taiwan 2009–2010	Prospective case–control	1 year	Emergency department	65	Risk factors	Number of drugs (AOR 4.1, 95% CI 2.4–6.9 for 3–7 drugs; AOR 6.4, 95% CI 3.7–11.0 for eight or more drugs) and increased concentration of serum creatinine (AOR 1.5, 95% CI 1.1–2.2)

Study	Country and year conducted	Design	Duration	Settings	Mean/ median age (Years)	Main outcome measures	Predictors/risk factors
Zhang et al. [8]	Australia 2005	Retrospective cohort	Records of ADR admission from 1980 to 2000 and followed for three years	All public and private hospitals	Mean age not reported, study in patients aged ≥60 years	ADR predictors	Sex (HR 1.08, 95% CI 1.02–1.15, for men) First admission in 1995–1999 (HR 2.34, 95% CI 2.00–2.73) Length of hospital stay (HR 1.11, 95% CI 1.05–1.18, for stays ≥14 days) CCI (HR 1.71, 95% CI 1.46–1.99, for score ≥7) Comorbid congestive cardiac failure (HR 1.56, 95% CI 1.43–1.71), peripheral vascular disease (HR 1.27, 95% CI 1.09–1.48), chronic pulmonary disease (HR 1.61, 95% CI 1.45–1.79), rheumatological disease (HR 1.65, 95% CI 1.41–1.92), mild liver disease (HR 1.48, 95% CI 1.05–2.07), moderate to severe liver disease (HR 1.85, 95% CI 1.18–2.92), moderate diabetes (HR 1.18, 95% CI 1.07–1.30), diabetes with chronic complications (HR 1.91, 95% CI 1.65–2.22), renal disease (HR 1.93, 95% CI 1.71–2.17), any malignancy including lymphoma and leukaemia (HR 1.87, 95% CI 1.68–2.09), and metastatic solid tumors (HR 2.25, 95% CI 1.92–2.64)

Abbreviations: ADR, adverse drug reaction; OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; AOR, adjusted odds ratio; HR, hazard ratio.

Age as a significant contributing factor to ADR-related hospitalisation had been observed in community-dwelling older patients in some studies [4, 175, 176]. The odds of experiencing severe ADRs increased by 3% per 1-year increase in age above 66 years [175].

The number of drugs being taken has also been highlighted in many studies as an independent risk factor for ADR-related hospital admissions [4, 87, 169, 172, 175, 176, 188-191]. It has been estimated that the chance of an older patient having an ADR increases from 10%, when one medication is used, to 75% if more than five medications are used concurrently [192]. The risk increase of an older patient (mean age 70 years) having an ADR-related hospitalisation is 24% for each drug increase [4].

The prevalence of multimorbidity (the coexistence of multiple chronic diseases) in older patients ranges from 55% to 98% based on the systematic reviews [18]. The presence of comorbidity also predicted ADR-related hospitalisation in community-dwelling older patients [4, 8, 96, 175, 191]. Relevant comorbidities included ischaemic heart disease; heart failure; depression; diabetes; peripheral vascular disease; and pulmonary, rheumatological, hepatic, renal, and malignant diseases. In a population-based retrospective study, comorbidity predicted repeat admission for ADRs in older patients, especially those with comorbidities often managed in the community [8].

Potentially inappropriate drug prescribing is highly prevalent among community-dwelling older patients, and potentially inappropriate medications (PIMs) in these patients are significantly associated with ADRs and subsequent hospital admission [193, 194]. According to Price et al., exposure to a PIM from the Beers list of medications was associated with a significant increase in unplanned hospitalisations (odds ratio [OR] 1.18, 95% confidence interval [CI] 1.15–1.21) [195]. There was also an increase in inpatient

visits (OR 1.99, 95% CI 1.76–2.26) in older patients who were prescribed PIMs based on a retrospective cohort study [196].

A range of other factors has also been associated with ADR-related hospitalisation, but these associations have been less consistently described. The presence of drug interactions was identified as a risk factor for ADRs in one study [173]. Female sex was also associated with ADR-related hospitalisation in older patients based on a study by Onder et al. [4]. However, sex was not found to be an independent risk factor based on a cross-sectional study [176]. An overview of the predictors of ADR-related hospitalisation in older patients is provided in Table 5.

Table 5. An overview of predictors of ADR-related hospital admission in the elderly

Frequently reported predictors	Other predictors
Number of medications	Drug interactions [173]
[4, 87, 169, 172, 175, 176, 188-191]	Female sex [4]
Comorbid conditions [4, 96, 175, 191, 197]	Self-medication [188]
Age [4, 175, 176]	Use of antithrombotics [188]
Potentially inappropriate medications	Use of antibacterial drugs [188]
[195, 196]	Alcohol use [4]
	Falls before admission [172]
	Patients living alone [189]
	Increased serum creatinine [190]
	Multiple pharmacy visits [175]
	More than three consulting physicians [189]
	Newly prescribed drugs [175]
	Recent hospital admission [175]
	Long-term care residence [175]
	Patients with diabetes or neoplasms [189]
	Gastrointestinal bleeding or haematuria [172]
	Ischaemic heart disease [96]
	Depression [96]
	Heart failure [96]

Abbreviation: ADR, adverse drug reaction.

2.9. The need for an ADR prediction tool in older patients in primary care

Prediction tools use multiple predictors to estimate the absolute risk that a certain outcome is present and enable the stratification of individuals or group of individuals by these risks [198]. They are usually developed to guide health care professionals in their decision making regarding further management and to inform individuals about their risk of experiencing a certain outcome [199]. Risk prediction models for ADRs have begun to emerge in recent years, which aim to assist health care professionals to make clinical and therapeutic decisions to minimise the risk of drug-related harm, especially in the older population having the highest risk of ADRs [9, 10, 167]. This will help the physician and the pharmacist to pay extra attention to a patient's medications when they are identified as being at risk [9].

It is often difficult to predict the occurrence of ADRs in older patients for several reasons. The presentation of an ADR is often atypical and nonspecific in nature, which can be misinterpreted as a new medical problem or a complication relating to a preexisting diagnosis [200]. This may lead to the addition of another drug to treat the symptoms (referred to as a "prescribing cascade" [201]), which will again increase the risk of drug–drug interactions and another ADR [202]. Sometimes, due to inappropriate polypharmacy, there is a chance that two or more drugs taken by the patient may lead to the same ADR [203]. The prediction of ADRs is especially challenging in patients with dementia, and cognitive impairment since problems with the patient's communication and reporting of adverse effects might reduce the clinician's ability to detect ADRs [204]. Hence, identification of the various risk factors for ADRs and predicting high-risk elderly patients is essential for better therapy outcomes and targeting additional resources toward this group [9]. To our knowledge, there are no empirical data that allow stratification of

community-dwelling older people according to the likelihood of ADRs leading to hospital admission. A fundamental problem is that there is only a limited understanding of the risk factors associated with ADR-related hospitalisation in the older population living in the community. Also, considerably more research has been focused on ADRs occurring in the hospital than in the community setting [205].

The contemporary validated ADR risk prediction tools used in hospital settings, detailed in Table 6, could be used as guides to develop similar models in community settings. The GerontoNet ADR risk score is one such validated model proposed by Onder et al. to identify hospitalised patients who are at an increased risk of an ADR [9]. This risk score identified several risk factors for the development of ADRs and developed a score that allows stratification of patients according to the likelihood of an ADR. The strongest predictors of ADRs in this study were the number of medications and a history of an ADR, followed by the presence of heart failure, liver disease, four or more medical conditions, and renal failure. The GerontoNet ADR risk score was reported to have satisfactory predictive value for ADRs with an area under the curve (AUC) of 0.71 (95% CI 0.68–0.73) [9, 167]. But, one of the important limitations of this study was that data on the preventability of ADRs were not collected, so the authors could not assess the risk factors for preventable ADRs. Also, these study findings cannot be extrapolated to older patients living in the community setting since the data were collected based on hospitalised patients 65 years or above. Another important limitation is that the GerontoNet ADR risk score did not account for the use of PIMs as a risk factor, which could be a stronger predictor of ADRs.

Table 6. Features of validated ADR prediction tools for elderly hospitalised patients

Features	Onder et al. [9] (GerontoNet ADR risk score)	Tangiisuran et al. [10] (BADRI) model
Study design		
Developmental stage	Retrospective cohort	Prospective cohort
Validation stage	Prospective cohort	Prospective cohort
Main outcome measure	ADR (6.5%)	ADR (12.5%)
Age of study participants (years)	Mean (SD)	Median (IQR)
	78 (7.2)	85 (81–89)
Most common ADRs	Cardiovascular and arrhythmic complications	–
Predictors of ADRs	≥4 Comorbid conditions	≥8 drugs
	Heart failure	Hyperlipidaemia
	Liver disease	Raised white cell count
	Number of drugs	Use of antidiabetic agents
	History of ADR	
	Renal failure	Length of stay ≥12 days
Predictive ability of risk score (AUROC)		
Developmental stage	0.71 (95% CI 0.68–0.73)	0.74 (95% CI 0.68–0.79)
Validation stage	0.70 (95% CI 0.63–0.78)	0.73 (95% CI 0.66–0.80)
Cut-off score	Between 3 and 4	>1
Sensitivity	68%	80%
Specificity	65%	55%

Abbreviations: ADR, adverse drug reaction; AUROC, area under the receiver operating characteristic curve; CI, confidence interval; SD, standard deviation; IQR, interquartile range.

O’Connor et al. investigated the clinical applicability and the ability to predict ADRs using the GerontoNet ADR risk score in hospitalised older patients [167]. The variables that increased ADR risk in their alternative model included renal failure, increasing number of medications, inappropriate medications, and age ≥75 years. The study results showed that 37.7% of ADRs were not predicted by the GerontoNet ADR risk score. The authors’ model included additional predictors like PIMs which would influence the presence of ADRs, but had a lower predictive value for ADRs (AUC of 0.62 [95% CI 0.57–0.68]) compared to the GerontoNet ADR risk score.

Tangiisuran et al. recently developed and validated an ADR risk model in a population of patients with a median age of 85 years [10]. This model was based on five clinical variables, some of which have not been previously reported. Compared with the GerontoNet ADR risk score and the model developed by O’Connor et al., this model had a higher predictive value for ADRs. Again, this model did not account for the use of PIMs as a risk factor. Also, this model did not use a uniform criterion for causality assessment of ADRs, which might have affected the outcome of the study.

The utility of an ADE trigger tool had been explored in a few studies conducted among older patients living in the community. One such tool used a 39-item trigger tool in patients aged 65 years or above in ambulatory primary care practices [206]. The most common triggers and their positive predictive values (PPVs) for ADE were “Medication stop” (26.3%), “Hospitalisation” (21.8%), and “Emergency Room visit” (14.9%). Most of the triggers had very low PPVs, and only nine of the triggers had PPVs >5% which could detect 94.4% of the ADEs. Similarly, the utility of an ADE trigger tool in Veterans Affairs nursing homes has also been studied and found an overall PPV of 40.1% [207]. The most common ADEs detected by this tool were acute kidney injury, hypokalaemia,

hypoglycaemia, and hyperkalaemia. Even though these tools could be used to identify ADEs in community-dwelling older patients, there is a clear need to predict the future occurrence of these events, especially ADRs.

2.10. Development of an ADR prediction tool for older patients in primary care

A study has suggested that the majority of older patients had their own family physicians (95%) at the time of presenting to the ED due to ADRs [175]. Primary care physicians are best able to understand the complete medical, functional, and social issues that are in play when optimising medications in older people living in the community. Since the older population is likely to have multiple risk factors for ADRs, ideally, the GPs should be able to predict those older adults who have a severe risk of ADRs that may lead to emergency hospital admissions. The development of an ADR prediction tool in community settings would facilitate this. The design of such a tool would require identification of a comprehensive list of possible predictive factors contributing to ADR-related hospitalisation based on the literature, available validated ADR prediction tools and clinical experience. These predictive factors could then be quantified in large populations of elderly subjects admitted and not admitted to hospital with an ADR preferably using a prospective study design. Univariate and multivariate analyses could be undertaken, and the significant predictors of ADR-related hospitalisation assigned a score based on their respective ORs. Finally, an ADR risk score could be computed based on the sum of the scores of individual variables as described by Onder et al., with a subsequent validation stage [9]. A risk score may also be used to improve prescribing practice. The ADR risk score could potentially be integrated into prescribing software to alert GPs regarding their patients' risk of ADRs and prompt appropriate preventive

measures, which might include medication review in high-risk patients, avoiding inappropriate medications, comprehensive geriatric assessment, [3] and cessation of high-risk medications which are least likely to be beneficial. Similarly, policy makers could use the score to target limited health care resources to patients in real need of intervention to address the issue of quality use of medicines.

2.11. Conclusion

It is clear that older patients are at significant risk of hospital admissions due to ADRs and many ADRs occurring in this population are considered preventable. There is a need for greater understanding of the predictors of ADRs in these patients, and how these predictors are interrelated. This will provide the basis for improved risk assessment practices. Even though various risk models in older populations have been suggested for use in hospital settings, there is a clear need for a simple, practical, and efficient tool to identify the high-risk group of older patients most likely to be admitted to hospital due to ADRs. These patients can be targeted in order to reduce their risk of ADRs and their associated morbidity and costs.

CHAPTER THREE

3. Adverse Drug Reaction-Related Hospitalisation in Elderly Australians: A Prospective Cross-Sectional Study in Two Tasmanian Hospitals

3.1. Preface

Chapter 2 highlighted the need for a validated adverse drug reaction (ADR) tool to identify high-risk elderly patients most likely to be admitted to hospital due to ADRs. To better inform the design of such a tool, we needed to enhance our understanding of ADRs that lead to hospitalisation. Hence, this chapter describes the results of a descriptive analysis, which pooled the available data from two prospective studies that were conducted to develop and validate an ADR prediction tool. This descriptive analysis enabled us to understand the current extent of the problem of ADR-related admissions in elderly Australians before the development of a validated ADR tool.

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3.2. Abstract

Introduction*:* Adverse drug reactions (ADRs) have been commonly cited as a major cause of hospital admissions in older individuals. However, despite the apparent magnitude of this problem, there are limited prospective data on ADRs as a cause of hospitalisation in elderly medical patients.

Objectives: The objective of this study was to evaluate the proportion, clinical characteristics, causality, severity, preventability, and outcome of ADR-related admissions in older patients admitted to two Tasmanian hospitals.

Methods: We conducted a prospective cross-sectional study at the Royal Hobart and Launceston General Hospitals in Tasmania, Australia. A convenience sample of patients, aged 65 years and older, undergoing unplanned overnight medical admissions was screened. ADR-related admissions were determined through expert consensus from detailed review of medical records and patient interviews. The causality, preventability, and severity of each ADR-related admission were assessed.

Results: Of 1,008 admissions, the proportion of potential ADR-related medical admissions was 18.9%. Most (88.5%) ADR-related admissions were considered preventable. Cardiovascular complaints (29.3%) represented the most common ADRs, followed by neuropsychiatric (20.0%) and renal and genitourinary disorders (15.2%). The most frequently implicated drug classes were diuretics (23.9%), agents acting on the renin angiotensin system (16.4%), β-blocking agents (7.1%), antidepressants (6.9%) and antithrombotic agents (6.9%). Application of the Naranjo algorithm found 5.8% definite,

70.1% probable and 24.1% possible ADRs. ADR severity was rated moderate and severe in 97.9% and 2.1% of admissions, respectively. For most (93.2%) ADR-related admissions the ADR resolved, and the patient recovered.

Conclusion: Hospitalisation due to an ADR is a common occurrence in this older population. There is need for future studies to implement and evaluate interventions to reduce the risk of ADR-related admissions in elderly populations.

Key Points

- Almost one in five unplanned overnight hospital admissions to medical wards in elderly Australian patients were related to ADRs.
- Most ADRs were preventable, and cardiovascular medications were commonly implicated.
- In the majority of patients, ADR-related admissions were caused as a result of a combination of two or more drugs sharing a similar ADR profile (e.g., hypotension).

3.3. Introduction

Adverse drug reaction (ADR) rates in the USA increased between 1999 and 2006, with higher ADR death rates observed among elderly individuals [68]. It has also been estimated that ADRs cause 100,800–197,000 deaths annually in the European Union [45], while a considerable proportion (5.6%) of all unplanned admissions were medication-related based on a multicentre prospective study in The Netherlands [208]. An Australian study found that hospital admissions due to ADRs in elderly patients had increased despite programs to promote rational and safer use of medicines [5]. Elderly people are particularly vulnerable to ADRs due to an increased chronic disease burden, polypharmacy (concomitant prescription of five or more drugs [209]), and age-related physiological changes affecting the pharmacokinetics and pharmacodynamics of drugs [9, 86, 210]. Although one of the more serious outcomes of ADRs in elderly people living in the community is hospitalisation, data on the occurrence of these events are often not well-documented and difficult to obtain [169, 175].

Prospective studies allow more accurate recording of both drug history and symptoms to assess the causality of ADRs [58]. Pirmohamed et al. [58] conducted a large prospective analysis of ADR-related hospital admissions in two large general hospitals in the UK (2001–2002) and found that patients admitted with ADRs (median age 76 years) were significantly older than hospitalised patients without ADRs (median age 66 years) [58]. The majority of other prospective studies [86] on ADR-related admissions in the elderly were conducted in specialist settings (geriatric/emergency departments), rather than general medical settings. Furthermore, few studies have utilised patient interviews to complement ‘intensive monitoring’ [37] in identification of ADRs and assessment of ADR preventability. Franceschi et al. [173] and Conforti et al. [174] conducted

prospective studies in Italy (2004–2005 and 2009, respectively) and found 6–11% of admissions to a geriatric unit were due to ADRs. De Paepe et al. [211], Olivier et al. [188], and Ma et al. [212] conducted prospective studies in Belgium (2007), France (2002–2003) and China (2008–2011), respectively, and found 7–30% of admissions to an emergency department were due to ADRs. From an Australian perspective, Chan et al. [88] conducted a prospective cross-sectional survey in 1998 at the Royal Hobart Hospital (RHH) and found that 13.3% of admissions to medical wards were ADR-related, although this study was small relative to other studies.

Given the scarcity of ADR-related hospital admissions data in the elderly identified using intensive monitoring, and the lack of recent data from Australia, additional prospective studies on elderly ADR-related admissions are needed. Hence, our aim was to ascertain the proportion of ADR-related medical admissions in older patients admitted to Tasmanian hospitals, identify the commonly implicated drugs, describe the clinical manifestations and outcomes of these ADRs, and determine their causality, preventability, and severity.

3.4. Methods

This prospective cross-sectional study was carried out at two tertiary care hospitals in Tasmania, Australia: the Royal Hobart Hospital (RHH) and Launceston General Hospital (LGH). The RHH is Tasmania's largest public acute care hospital for Southern Tasmanians (500-bed capacity in a population of approximately 250,000). The LGH provides acute care for the northern region of Tasmania (300-bed capacity in a population of approximately 87,000). Both hospitals are within the Tasmanian Health Service and provide a comprehensive range of general and specialty medical and surgical services.

The majority of patients in both hospitals are seen by clinical pharmacists on the wards, who undertake an admission medication history and reconciliation as per national standards [213]. The best possible medication history is collected from the patients and their relatives and/or caregivers, their general practitioner (GP), and/or community pharmacy. This information is entered into a state-wide hospital medication management system available for all staff to access across the state. The patients' previous admission/discharge details are also stored as an electronic patient file or digital medical record, which could also be accessed during the study for any missing information.

The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (Appendix 1), and study participants provided written informed consent (Appendix 2). The data presented here were collected as part of the PADR-EC (Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients) study, which has been published elsewhere [214]. The previous paper reported on the derivation of the prediction score from the RHH cohort and the validation of the dataset in the LGH cohort. In the present analysis, we pooled the available data to create a larger dataset to allow us to report on the proportion of ADR-related hospital admissions in older patients admitted to Tasmanian hospitals, identify commonly implicated drugs, and describe the clinical manifestations and outcomes of ADRs.

A convenience sample of community-dwelling patients aged ≥65 years with acute, unplanned admissions to the medical wards of the RHH and LGH was included in the study. Data were collected from March 2014 to March 2015 at the RHH and from September 2015 to December 2015 at the LGH. Exclusion criteria included an inability to be interviewed due to their medical condition (e.g., patients with infections in isolation,

a terminal illness, or a hearing impairment or low vision), refusal to participate, or unavailability of medical records.

We assessed each patient to determine whether the admission was potentially due to an ADR. An ADR was defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [36, 37]. This definition excludes therapeutic failures, under-treatment, intentional and accidental poisoning (i.e., overdose), and drug abuse. ADRs that were observed during the hospital stay were excluded. All elderly admissions to the medical wards between Monday and Friday (9 am-5 pm) were identified by the primary clinical pharmacist researcher (NPN) using computerised admission entry details. Patients were followed until discharge to collect sufficient information for the final assessment of the ADR. All data were collected manually using a data collection form (Appendix 3) and later transferred into a Microsoft Access® database (Microsoft Corporation, Redmond, WA, USA). Each ADR contributing to the patient admission was assessed if the symptoms of admission were consistent with the known adverse effect profile of the drug/drugs (according to the *Australian Medicines Handbook*, or UpToDate database [215, 216]) and, after investigation, other causes were excluded [58]. The assessment of whether a certain drug/drugs may have caused or contributed to an acute admission was determined through expert consensus from comprehensive review of medical records and patient interviews. The patient interviews were conducted in the presence of their family members using a pre-tested structured questionnaire (Appendix 4). During the recruitment process, we initially tested the questionnaire in a small sample of patients and structured it to suit the patients' understanding of specific questions. Questions that patients found difficult to

answer (e.g., recent drug changes, previous history of ADRs) were confirmed with family members. These data were verified using the detailed medication reconciliation notes from clinical pharmacists, GPs' medical records if available, and other patient history notes by nurses and doctors. Patients who could not be interviewed due to their illness at the time of their admission were interviewed at a later stage of their hospital stay. All patients initially categorised as having an ADR-related admission by the clinical pharmacist researcher (NPN) and a random selection of 10% of cases without a suspected ADR-related admission were independently and blindly assessed by a senior clinical pharmacist (MC). The clinical pharmacists met to reach a consensus decision regarding the presence of an ADR-related admission, causality, and preventability and subsequently excluded the doubtful cases. This method of ADR assessment had been reported in previous studies [169, 208, 217]. During expert consensus, the average time spent for assessment of ADR cases was 15–30 min per case. The causality of the relation between drug use and ADRs were determined using the Naranjo algorithm (Appendix 8) [179]. ADRs were classified as definite (score from 9 to 12), probable (score from 5 to 8), possible (score from 1 to 4) or doubtful (score from 0 to -2) and only definite, probable, and possible ADRs were considered for this study. We assessed the causality of each suspected ADR [4, 218] and of the ADR-related admission [58, 173]. When a patient had multiple ADRs, we used the ADR with the highest score using the Naranjo algorithm for further analysis [172].

The Anatomical Therapeutic and Chemical (ATC) classification was used to code the medications taken before hospital admission [219]. We determined the preventability of the ADRs using the modified Schumock and Thornton criteria [220, 221], as follows:

- The drugs were not appropriate for the patient's condition;
- The dose, frequency, and route of administration were inappropriate for the patient's age, weight, or disease state;
- Therapeutic drug monitoring or other necessary laboratory tests were not performed;
- The patient had a history of allergy or previous reaction to the administered drug;
- A documented drug interaction was involved in the ADR;
- A serum concentration above the therapeutic range was documented;
- Non-compliance was involved in the ADR; or
- A medication error was the cause of the reaction.

We assessed the preventability of each suspected ADR [218] and the preventability of the ADR-related admission [58]. When a combination of drugs was involved, but the preventability varied for each drug, the preventability of the ADR was assessed as that for the drug scoring the highest grade of preventability [88].

The severity of ADRs was determined using the Hartwig et al. scale (Appendix 9) [222]. Severe reactions were defined as those that were life-threatening, caused permanent damage, or required intensive care. Moderate reactions were those requiring hospital admission, change in therapy, or specific treatment. Although this classification also includes a definition for mild ADRs, all ADRs in this study at least resulted in hospital admission and were therefore only classified as either moderate or severe.

We grouped ADRs as Type A and Type B reactions based on the Rawlins and Thompson [223] classification and whether it was due to any drug–drug interactions (DDIs), including with any 'over-the-counter' (OTC) medications, as evaluated

according to the UpToDate database (Lexi-Interact™ Online) [216]. Type A reactions were defined as dose-dependent reactions as an exaggeration of a drug's normal pharmacological actions, and Type B reactions were dose-independent and unpredictable. A drug interaction was defined as the modification of one drug by the prior administration of another, producing loss of therapeutic effect or toxicity [88]. The UpToDate database assigns each DDI a risk rating of A (no known interaction), B (no action required), C (monitor therapy), D (consider therapy modification), or X (avoid combination). The outcome of the ADR-related admission was categorised as recovery (i.e., patients were clinically stable at discharge), death or unknown.

Data were analysed descriptively and presented as median (interquartile range [IQR]) or number (%) based on type and distribution of data. Analyses were performed using SPSS® version 20.0 (SPSS Inc., Chicago, IL, US).

3.5. Results

A total of 1789 elderly patients were screened and 781 (43.7%) were excluded either due to their unwillingness to consent (253 patients) or inability to be interviewed due to the severity of their medical condition (528 patients). The remaining 1008 patients were enrolled in the study (RHH, 768 patients; LGH, 240 patients). The characteristics of the study population are summarised in Table 7 and Appendix 5. The median age of the participants was 81 years (IQR 74–86) and the median number of medications (including OTC medications) taken at the time of admission was ten (IQR 7–14). Most (89.0%) were taking five or more medications. Males and females were almost equally distributed. The patients' characteristics were comparable in both hospitals [214].

Table 7. Principal characteristics of the study population (n=1008)

Characteristic	Value
Age in years [median (IQR)]	81 (74–86)
Length of stay in days [median (IQR)]	5 (3–10)
Female (%)	53.4
Use of alcohol * (%)	37.4
Smoker (%)	10.7
Number of drugs taken at the time of admission [median (IQR)]	10 (7–14)
Number of co-morbid conditions [median (IQR)]	5 (4–7)
Drug changes in the preceding three months (%)	49.4
Use of OTC medications (%)	44.0
Use of herbal medicines (%)	23.2
Living status (%)	
Alone	*40.6*
With family or friends	*56.3*
Nursing home	*3.1*
Medical history (%)	
Cardiovascular disease	89.1
Renal failure	52.7
Anaemia	43.9
Vascular disease	39.6
Hyperlipidaemia	31.2
Diabetes	30.3
Chronic obstructive pulmonary disease	29.5
Cancer	24.4
Cerebrovascular disease	17.7
Depression	12.8
Falls	5.1
Dementia	6.8

Characteristic	Value
Other variables (%)	
Regular GP visits	93.0
Assistance required with ≥1 activity of daily living	65.4
Previous ADR	58.3
Presence of ADR within past three months	16.7
HMR in preceding three months	6.3

Abbreviations: ADR, adverse drug reaction; GP, general practitioner; HMR, Home Medicines Review; IQR, interquartile range; OTC, over-the-counter.

* More than two standard drinks daily [224].

Of the 1008 patients examined, ADRs potentially caused or contributed to 191 (18.9%) acute medical admissions. Participants with an ADR had a median age of 82 years (IQR 73–86) and 54.5% were females. The median number of medications taken at the time of admission was 11 (IQR 8–15), and the median length of hospital stay was six days (IQR 3–12). Among the 191 patients with ADRs, 83 (43.5%) were using OTC medications and 43 (22.5%) were using herbal medications; no ADRs to these medications were identified. Of the 191 patients, 108 (56.5%) had a history of previous ADRs, and in 102 (94.4%) of these patients, the medications were altered after the last ADR was experienced. Only two (1.1%) patients were admitted with the same ADR (rash induced by furosemide and dizziness induced by pregabalin) as previously reported.

Of the 191 patients with potential ADRs, 100 (52.4%) had a single ADR; 62 (32.5%) had two ADRs; 18 (9.4%) had three ADRs; six (3.1%) had four ADRs; four (2.1%) had five ADRs, and one (0.5%) had six ADRs. In 58 (30.4%) cases the ADRs were caused by a single drug, and in 133 (69.6%) cases the ADRs were caused by a

combination of drugs. Also, in the majority (123 [64.4%]) of cases, a combination of two or more drugs sharing a similar ADR profile (e.g., hypotension) caused the ADR-related admissions. Thus, a total of 328 ADRs caused by 452 drugs contributed to all ADR-related admissions. Applying the Naranjo algorithm to the 328 ADRs, there were 27 (8.2%) definite ADRs, 208 (63.4%) probable ADRs, and 93 (28.4%) possible ADRs. When only the one highest scoring ADR per patient was considered, 11 (5.8%) patients had definite ADRs, 134 (70.1%) had a probable ADR, and 46 (24.1%) had a possible ADR.

The most frequently involved drug classes were cardiovascular drugs (269 [59.5%]), followed by drugs acting on the nervous system (100 [22.1%]) and antithrombotic agents (31 [6.9%]). Among the cardiovascular drugs, diuretics (108 [23.9%]), agents acting on the renin–angiotensin system (74 [16.4%]), and β-blockers (β-adrenoceptor antagonists) (32 [7.1%]) were frequently implicated in causing ADRs (Appendix 6). Antidepressants (31 [6.9%]) and opioids (22 [4.9%]) were the most frequently implicated centrally acting drugs. Considering individual drugs, furosemide was the most common drug responsible for ADRs (61 [13.5%]), followed by perindopril (19 [4.2%]), metoprolol (15 [3.3%]), candesartan (15 [3.3%]), and amitriptyline (14 [3.1%]).

The type of ADRs observed in the study cohort, and the most frequently implicated drugs are presented in Table 8. The most common manifestations of ADRs were cardiovascular (96 [29.3%]), neuropsychiatric (72 [20.0%]), renal and genitourinary (50 [15.2%]), and haematological (35 [10.7%]) in nature (Appendix 7)

Table 8. Adverse drug reactions contributing for hospital admission and the drugs most potentially implicated

Type of ADR (*n*=328)*	***n* (%)**	**Most common clinical presentation of ADR***	***n* (%)**	**Most common drugs implicated***
Cardiovascular	96 (29.3)	Hypotension/orthostatic hypotension/syncope	64 (33.5)	Diuretics, RAS inhibitors, β-blockers (β-adrenoceptor antagonists), calcium channel blockers (antagonists)
		Bradycardia	12 (6.3)	β-Blockers
Neuropsychiatric	72 (20.0)	Dizziness	44 (23.0)	Diuretics, β-blockers, calcium channel blockers, RAS inhibitors, antidepressants
		Confusion	14 (7.3)	Benzodiazepines, opioids, anticonvulsants, antidepressants
Renal and genitourinary	50 (15.2)	Acute kidney injury	49 (25.7)	Diuretics, RAS inhibitors
Haematological	35 (10.7)	Haemorrhage	22 (11.5)	Antiplatelets, anticoagulants
Endocrine and metabolic	30 (9.1)	Hyperkalaemia	11 (5.8)	RAS inhibitors
		Hyponatremia	11 (5.8)	Diuretics
Gastrointestinal	24 (7.3)	Nausea and vomiting	8 (4.2)	Cardiac glycosides
Neuromuscular and skeletal	12 (3.7)	Myalgia	4 (2.1)	HMG-CoA reductase inhibitors (statins)
Others	9 (2.7)	Infections	5 (2.6)	Immunosuppressants

The fourth column represents the number and percentage of patients (total number of ADR-related admissions = 191) who experienced the most common clinical presentation of ADR.
Abbreviations: ADR, adverse drug reaction; RAS, renin–angiotensin system.
* Multiple drugs were suspected to be involved in some ADRs, or one drug might have contributed to multiple ADRs.

Of the 328 ADRs, 286 (87.2%) were assessed as preventable. When the preventability of ADR-related admissions was assessed based on the highest grade of preventability, 169 (88.5%) ADR-related admissions were considered preventable. Overall, 187 (97.9%) of ADR-related admissions were classified as moderately severe, while only 4 (2.1%) were severe. Of the 191 ADR-related admissions, the ADR resolved in 178 (93.2%) and the patient recovered, while in four cases (2.1%) the outcome was fatal and in nine cases (4.7%) the outcome was unknown due to the patient's transfer to another hospital. The severe ADRs that contributed to the four deaths were 'probable' ADRs and these included digoxin toxicity, pancytopenia related to antiplatelets (aspirin) in combination with other drugs (methotrexate, hydroxychloroquine), hypotension caused by a combination of diuretic (furosemide), ACE inhibitor (ACEI) (perindopril) and a β-blocker (carvedilol), and acute kidney injury related to the combination of an ACEI (fosinopril) and a diuretic (indapamide) (glomerular filtration rate on admission was 7 mL/min). The patients who were admitted with digoxin toxicity and pancytopenia died due to hospital-acquired pneumonia and multiple organ failure, respectively. The patient admitted due to severe hypotension eventually died because of arrhythmia. Multiple organ failure was the reason of death in the patient admitted with acute kidney injury.

A total of 181 DDIs were potentially involved in 82 (42.9%) of the ADR-related admissions. Of 181 DDIs observed, 131 (72.4%) were assigned a risk rating of C, 48 (26.5%) a risk rating of D, and two (1.1%) a risk rating of B. Examples of DDIs included confusion caused by multiple nervous system depressants, hypotension caused by multiple blood pressure-lowering agents, bleeding caused by clopidogrel and aspirin, and acute kidney injury associated with concomitant use of diuretics and ACEIs. All ADRs

were classified as Type A reactions except one ADR (rash induced by furosemide), which was considered a Type B reaction.

3.6. Discussion

We have conducted a prospective analysis of ADR-related hospital admissions in an elderly Tasmanian population. Our study found that approximately one in five unplanned admissions to medical wards were potentially due to ADRs in patients aged ≥65 years. A similarly high rate (17%) of ADR-related hospitalisations in the elderly was also found in a meta-analysis of 17 observational studies [101]. Determining the number of ADR-related admissions depends primarily on the methods used in their detection [98]. Prospective and intensive monitoring usually have the highest detection rate and can provide data not otherwise available [37, 85]. In other studies, the proportion of all hospital admissions due to ADRs has ranged from 3% to 20% [92, 96, 169, 172, 217, 225]. Differences in definitions of ADR, method of data collection, and target populations may account for the difference in these proportions [173]. In our study, the inclusion of all definite, probable and possible ADRs, together with a thorough review of ADR cases by the two expert clinical pharmacists, might have contributed to the identification of more ADRs. We interviewed all patients included in the study, in addition to reviewing medical records, to identify ADR-related admissions. Patient interviews by pharmacists identified more ADRs than spontaneous reporting by physicians and nurses in a previous prospective study [92]. There is also strong evidence that pharmacists report higher rate of adverse drug events than non-pharmacists [226].

Almost 90% of ADR-related hospitalisations were preventable, which is consistent with a subgroup meta-analysis demonstrating that 88% of ADR-related

hospitalisations in the elderly were preventable [101]. In other studies, the preventability varied from 37 to 77% [87, 169, 173]. Even though the preventability estimates vary across studies, it is evident that more than 50% of ADRs are preventable [56]. We found a predominance of ADRs due to Type A reactions resulting from known pharmacological actions, consistent with other studies [4, 58, 88, 96]. This study found 2.1% of patients had fatal outcomes due to ADRs. Fatal outcomes and increased length of stay in older patients due to ADRs have been observed in some studies [58, 173], and the proportion of severe ADRs was found to be as high as 18.6% in a prospective study [87]. A recent study found the crude in-hospital mortality rate was 10.2% in elderly patients with an ADR-related admission [225].

Our data showed that cardiovascular complaints, such as hypotension/orthostatic hypotension/syncope, were the most common ADRs resulting in hospital admission, and these results are consistent with other studies [88, 96, 212, 227]. This proportion may have been even higher if cases of dizziness associated with antihypertensives were also included. Some studies have reported gastrointestinal complaints as frequent ADRs causing admission [4, 173, 225], while haematological complaints were reported in other studies [188, 228]. Patients with cardiovascular disease are particularly vulnerable to ADRs due to their advanced age, polypharmacy, and the influence of heart disease on drug pharmacokinetics, such as a reduction in the volume of distribution and impairment of clearance, as seen in patients with congestive heart failure [229, 230]. Antihypertensive agents were the most frequent class of drugs responsible for ADR-related admissions, as found in other studies [4, 88, 96, 169, 174, 212, 217, 227]. Additionally, acute kidney injury (25.7% of admissions) was impacted by antihypertensive medications such as diuretics and agents acting on the renin angiotensin system. In other studies, the most

frequent therapeutic classes implicated in ADR-related admissions in the elderly were NSAIDs [4, 5, 173], antithrombotic agents [5, 173, 174, 188], or antidiabetic agents [188, 228]. The prevalence of orthostatic hypotension was very high (35–65%) in one international study in the elderly and significantly related to the number of concurrent causative medications [231]; elderly patients are also more prone to diuretic-induced dehydration and resulting orthostatic hypotension [232]. Our findings highlight the importance of cautious prescribing of antihypertensive agents, especially combinations of diuretics and agents acting on the renin–angiotensin system, in the elderly to prevent hypotension/orthostatic hypotension/syncope and acute kidney injury.

More than 50% of the ADRs identified in the present study were caused by a combination of drugs and most of our study participants were exposed to polypharmacy (five or more medications). Polypharmacy has been identified as an important potential risk factor for ADRs [4, 169, 172]. We also evaluated one important factor that has not been explicitly investigated in previous prospective studies, i.e., almost 65% of ADR-related admissions were caused by two or more drugs that share the same ADRs. Since some ADRs (e.g., hypotension) were particularly associated with simultaneous use of multiple medications with synergistic therapeutic and adverse effects, such as antihypertensives, prescribers need to be sure that the benefit of prescribing multiple similar medications is justified, to outweigh the risk of additive adverse effects of these agents. DDIs might have played a role in over 40% of ADR-related admissions, which is consistent with another prospective study in the elderly (32.3%) [173] and a cross-sectional study in which DDIs were suspected in 49% of cases [225]. These findings highlight the importance of obtaining an accurate medication history at each stage of a

patient's medication journey so that potential DDIs are not overlooked by their healthcare team.

Decreasing the medication burden in community-dwelling elderly patients will lead to reduced adverse events and improvement in health [233]. There is an increasing body of research demonstrating that deprescribing inappropriate or unnecessary medications is feasible, safe and can improve older patient's quality of life and decrease mortality [234, 235]. From our results, an obvious focus of deprescribing would be to reduce the number of different drugs with similar modes of action and/or adverse effects. Communication between health professionals such as a physician (geriatrician), nurse, and pharmacist enables optimal pharmacotherapy in elderly patients [210]. Clinical pharmacists can play a vital role, particularly at the point of discharge of elderly patients, to prevent ADR-related readmissions. In a randomised trial, pharmacist medication review, patient counselling, and telephone follow-up were associated with a lower rate of preventable adverse drug events after hospital discharge [138]. We also suggest implementing a comprehensive medication reconciliation at every transition point (admission, discharge, transfer) for the elderly, as suggested by the US Joint Commission on Accreditation of Healthcare Organisations [236].

The major strength of the study is that patients were prospectively included on admission and were followed up until discharge. We have also interviewed all the patients included in the study in addition to reviewing their medical records, which is different from a recent Spanish study [225] in which ADRs were identified either from the medical record or by direct patient interview. We also used a large sample from two major Tasmanian public hospitals, which allowed us to characterise the ADRs in a detailed manner, including their preventability. To our knowledge, many prospective studies on

ADRs have focused on patients admitted in a single hospital, and many studies did not assess the preventability of ADRs.

Our study has some limitations. The main limitation included the difficulty in determining the contribution of a certain drug/drugs to an acute admission due to ADRs. Some of the parameters for assessing the causality of ADRs, such as the inclusion of a re-challenge and use of placebo, could not be performed since they were not routine clinical practice. In addition, measurement of drug concentrations was not performed in most suspected ADRs. Another limitation was the collection of the data using convenience sampling. With limited resources, the study team relied on recruiting elderly patients whose availability coinciding with that of the primary clinical pharmacist researcher. The degree of generalisability of the study is restrained by this study design. In addition, we could not recruit some patients due to the severity of their medical conditions and these patients were perhaps at higher risk of admissions due to ADRs. A retrospective study could have included all patients, although such a study would lose the ability to obtain information through interview. While we believe that the study results might be generalisable to the Tasmanian elderly population, as well as in other states of Australia that have similar standards of health care delivery to the elderly, there are inherent limitations of convenience sampling. We suggest that further studies explore the burden of ADRs in elderly residing in other states of Australia. We could only review by consensus 10% of patients who were not admitted due to an ADR (controls), which may be another limitation of the study. This might have caused an underestimation of the ADR-related admissions even though the primary clinical pharmacist researcher assessed the cases and controls comprehensively and thoroughly. Participation of a physician might have provided a more comprehensive perspective to the assessment of ADRs [217],

although clinical pharmacists can play a major role in recognising drug-related problems in the elderly [21]. Finally, with limited resources, we could not assess whether patients had any sustained disability because of an ADR, despite being clinically stable at discharge.

Given the fact that the majority of the ADRs that resulted in hospitalisation were preventable in the present study, prevention of ADRs represents an important aim for physicians treating older patients [237]. Some strategies have been mentioned here, and these include medication review, avoiding use of inappropriate medications, and comprehensive geriatric assessment and management [3]. In order to ensure the cost effectiveness of such strategies, it would be necessary to target them to elderly patients who are at highest risk of ADR-related admission [238]. The recently developed PADR-EC score could facilitate identification of community-dwelling elderly people at risk of ADRs and subsequent ADR-related admission [214]. The PADR-EC score could potentially be integrated into a prescribing software at the point of patient discharge as well as in primary care to alert health care providers (primary care physicians, pharmacists, and nurses) to their patients' risk of ADRs and execute preventive strategies such as deprescribing.

3.7. Conclusion

Our research supports the findings from previous studies and further strengthens the evidence of ADRs as a cause of admissions in the elderly, along with updating the available information with respect to their proportion, preventability, outcome and clinical characteristics. Cardiovascular medications prescribed to elderly patients need thorough and regular scrutiny as these medications were frequently implicated in ADRs.

Improved medication management services in primary care are required to address the high rate of unnecessary hospitalisation due to preventable ADRs. Further research is needed to address the effectiveness of some interventions, such as deprescribing, in reducing the risk of ADR-related admissions in elderly populations.

CHAPTER FOUR

4. Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients (The PADR-EC Score)

4.1. Preface

The findings from Chapter 3 strengthened and updated the evidence relating to hospital admissions due to ADRs in elderly patients. The results also emphasised that this problem is persisting despite available prevention strategies. It is clear that additional strategies of ADR prevention are needed, and Chapter 2 discussed the need to investigate the utility of an ADR tool to identify high-risk elderly patients who are prone to ADR-related hospital admissions. Thus, we have developed and validated such a tool. The development and validation results of the ADR tool are presented in this chapter.

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4.2. Abstract

Background: Adverse drug reactions (ADRs) are the major cause of medication-related hospital admissions in older patients living in the community. This study aimed to develop and validate a score to predict ADR-related hospitalisation in people aged ≥65 years.

Methods: ADR-related hospitalisation and its risk factors were determined using a prospective, cross-sectional study in patients aged ≥65 years admitted to two hospitals. A predictive model was developed in the derivation cohort (n = 768), and the model was applied in the validation cohort (n = 240). ADR-related hospital admission was determined through expert consensus from comprehensive reviews of medical records and patient interviews. The causality and preventability of the ADR were assessed based on the Naranjo algorithm and modified Schumock and Thornton criteria, respectively.

Results: In the derivation sample (mean [±SD] age, 80.1±7.7 years), 115 (15%) patients were admitted due to a definite or probable ADR; 92.2% of these admissions were deemed preventable. The number of antihypertensives was the strongest predictor of an ADR followed by presence of dementia, renal failure, drug changes in the preceding three months and use of anticholinergic medications; these variables were used to derive the ADR prediction score. The predictive ability of the score, assessed from calculation of the area under the receiver operator characteristic (ROC) curve, was 0.70 (95% confidence interval (CI) 0.65–0.75). In the validation sample (mean [±SD] age, 79.6±7.6 years), 30 (12.5%) patients' admissions were related to definite or probable ADRs; 80%

of these admissions were deemed preventable. The area under the ROC curve in this sample was 0.67 (95% CI 0.56–0.78).

Conclusions: This study proposes a practical and simple tool to identify elderly patients who are at an increased risk of preventable ADR-related hospital admission. Further refinement and testing of this tool is necessary to implement the score in clinical practice.

4.3. Introduction

Advancing age contributes to increased drug usage in older patients, which in turn is associated with an increased risk of adverse drug reactions (ADRs), causing significant morbidity and mortality [173]. The prevalence of ADRs in older outpatient clinic attendees ranges from 5–35% [205, 239]. ADRs are also one of the main reasons for hospitalisation in older patients living in the community [169]. The proportion of all hospital admissions due to ADRs has ranged from 6–12% among older patients [96, 169, 172-174]. While individual risk factors for ADRs have been identified [4, 96], health professionals are not able to easily identify elderly community-dwelling outpatients who are at high risk of being hospitalised due to an ADR. More than half of ADR-related hospitalisations are considered preventable [88].

In recent years, risk prediction models for ADRs in elderly patients have begun to emerge, offering practitioners a potential tool to assist clinical and therapeutic decision making and facilitate targeting of additional resources toward this high-risk group [9, 10]. These tools were developed for use in secondary care hospital settings to help identify the risk of ADRs occurring during hospitalisation. To our knowledge, there is no prediction score available that has been developed for use in elderly patients with hospitalisation due to ADR (as opposed to ADRs that arise during hospitalisation) as the endpoint [238]. A tool developed that focussed on ADRs as a cause of hospitalisation could potentially be used in primary care and at the point of hospital discharge to prioritise primary care-based medication management services to prevent ADR-related morbidity and mortality in patients at the highest risk of such events. We aimed to develop and validate a prediction model for ADR-related hospitalisation in patients aged ≥65 years.

4.4. Methods

4.4.1. Derivation of a score to predict ADR-related hospitalisation

To develop the score [PADR-EC (Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients) score], a prospective cross-sectional study was conducted at the Royal Hobart Hospital (RHH), which is the major public acute care hospital in Southern Tasmania. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (Appendix 1), and study participants provided their written informed consent to participate in the study (Appendix 2). A convenience sample of all acute, unplanned, emergency admissions of patients aged ≥65 years admitted to medical wards over a period of 12 months (March 2014 to March 2015) were enrolled in the study. Patients were excluded if they were unwilling to participate, unable to be interviewed due to health or other reasons, or if their medical notes were not available for further investigation. The medical records of all consenting patients were reviewed within 48 hours of admission, and patients were interviewed as soon as practical after admission. Data collected included demographics, comorbidities, indicators of physical function and cognitive status, clinical diagnoses at admission, medications and medication changes prior to admission, previously documented ADRs, function in activities of daily living, social supports and living status. Patients and/or their relatives who were interviewed provided information about alcohol consumption, smoking status, recent hospital admissions, recent drug changes, drug allergies, use of over-the-counter (OTC) and herbal medicines, use of dosage administration aids, ADR occurrence within the last 3 months, regular pharmacy visits, and receipt of a Home Medicines Review (HMR), where a pharmacist conducts an interview with the patient regarding their medications and provides a report back to the general practitioner.

4.4.2. Predictive variables for ADR-related hospitalisation

Medications taken prior to admission were coded according to the Anatomical Therapeutic and Chemical codes [219]. Calculation of the number of medications was based on the number of active ingredients [96], where the active ingredients in combination products were also available as single-ingredient products. Clinical diagnoses and comorbidities were coded according to the International Classification of Primary Care, 2nd edition [240]. Comorbidity was measured using the Charlson comorbidity index (CCI) [241]. Renal failure was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2 or as documented in the medical records [242, 243]. Liver disease was defined as synthetic liver dysfunction or liver injury with raised transaminases greater than twice the normal range or documented liver disease [167]. Anaemia was defined as a haemoglobin concentration below 120 g/L in women and below 130 g/L in men [244]. All comorbidities were defined as present if documented in the medical records. Functional independence was measured using the Barthel index [245]. Potentially inappropriate medications (PIMs) were identified using the updated Beers criteria [147]. Each class of PIMs within the Beers criteria was individually assessed. Recent drug changes prior to hospital admission were determined. Recent drug change was defined as addition of a new drug or deletion of an existing drug (excluding 'when required' medications) or a change in drug doses in the three months preceding the patient's admission [246].

4.4.3. Identifying and assessing the presence of ADR-related hospitalisation

An ADR was defined as "a response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [37]. We assessed every consenting

patient during the study period to determine if the admission had been caused by an ADR. The reasons for hospitalisation are multifactorial in many cases [217], and therefore the determination of whether a certain drug/ drugs may have caused or contributed to an acute admission was based on comprehensive review of medical records and interview with the patient/relatives about their medication usage, including recent changes to drug therapy. The patients were interviewed in presence of their family members, and the response to specific questions (Appendix 4) were again verified using electronic patient file or digital medical records which contains all patient previous admission/discharge details. Comprehensive review of medical records included detailed review of medical and nursing records, medical record notes from primary care when available, medication reconciliation notes from clinical pharmacists, and an assessment of laboratory and other relevant clinical investigations. Patients were categorised as having an ADR if the cause of admission was consistent with the known adverse effect profile of the drug (according to *Australian Medicines Handbook*, or UpToDate database) [215, 216], if there was a temporal relation with the start of drug therapy and if, after appropriate investigations, other causes were excluded [247]. The clinical description of each ADR and the potential drug cause was collected, and the causality, preventability and eventual outcome of the suspected ADR-related hospitalisation were assessed. We also classified ADRs as Type A and Type B reactions, based on Rawlins and Thompson [223]. Type A reactions were defined as dose-dependent and predictable from the known pharmacologic action of the drug and Type B reactions if otherwise.

The Naranjo algorithm (Appendix 8) was used to assess the causality of the relation between drug use and hospitalisation [179]. ADRs were classified as definite (9–12 points), probable (5–8 points), possible (1–4 points), or doubtful (0 points). Only

definite and probable ADRs that provoked hospitalisation were considered for this study. ADRs observed during the hospital stay were excluded. The preventability of the ADR-related hospitalisation was assessed using the modified Schumock and Thornton criteria [220, 221]. These criteria included (1) the drugs were not appropriate for the patient's condition, (2) the dose, frequency and route of administration were inappropriate for the patient's age, weight or disease state, (3) therapeutic drug monitoring or other necessary laboratory test was not performed, (4) the patient had a history of allergy or previous reaction to the administered drug, (5) a documented drug interaction was involved in the ADR, (6) a serum concentration above the therapeutic range was documented, (7) noncompliance was involved in the ADR or (8) a medication error was the cause of adverse reaction. The ADR-related hospitalisation was considered to be preventable when it met any of these criteria.

All patients initially categorised as having an ADR-related admission, and a random selection of 10% of cases without a suspected ADR-related admission, were independently and blindly assessed by a senior clinical pharmacist for the presence and classification of an ADR-related admission. The primary researcher and the senior clinical pharmacist met to reach a consensus decision on the presence of an ADR-related admission and excluded doubtful cases. The cases thought to involve an ADR-related admission were also assessed blindly by the clinical pharmacist reviewer for causality, severity, and preventability. This review process had been used previously in similar studies [34, 217, 247]. The screening process and identification of ADR-related hospital admissions is outlined in Figure 2.

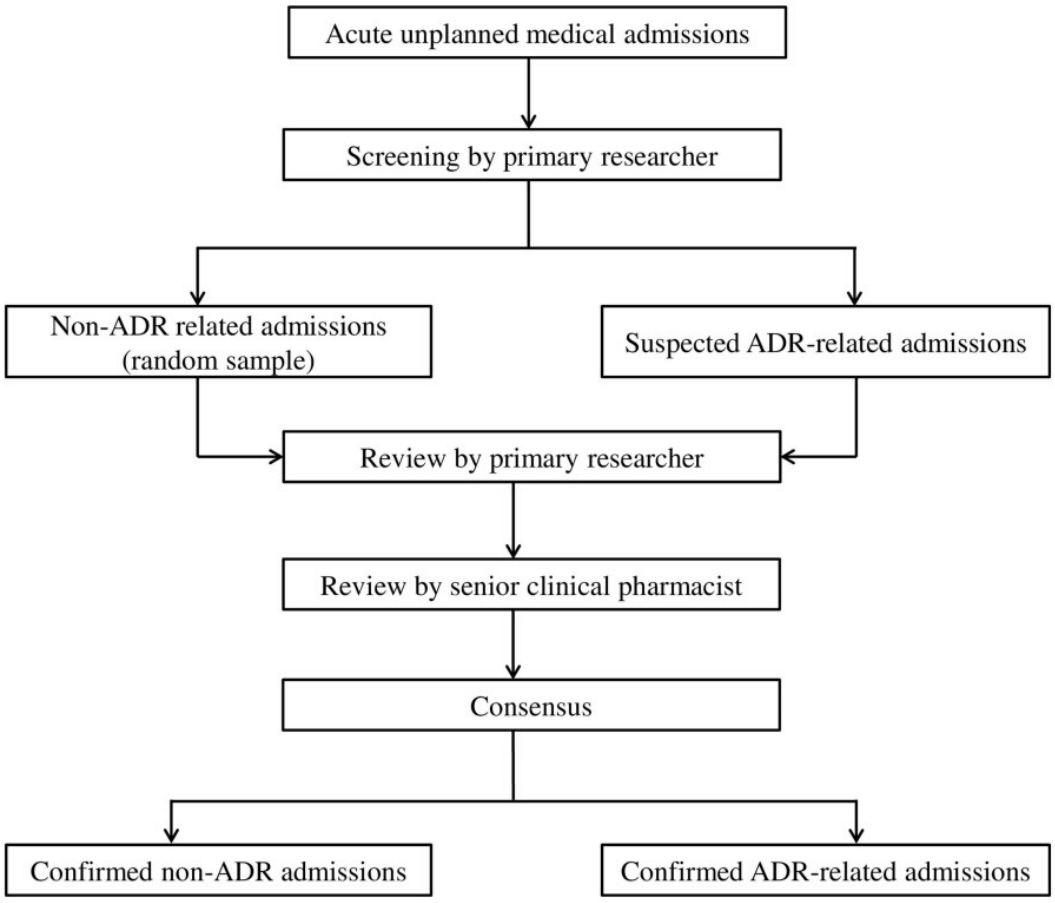

Figure 2. Diagram outlining the screening process of ADR-related hospital admission.

4.4.4. Statistical analysis

The PADR-EC score was developed in a similar manner to that described by Onder et al. [9]. Clinically relevant variables that are easily applied and practical for use in a primary care setting were considered. The chi-square test or Fisher's exact test were used to compare characteristics of those who experienced an ADR and those who did not. Variables identified as being associated with an ADR in the univariate analyses were entered into a binary logistic regression model. The variables with P values of <0.20 in the univariate analyses were candidates for inclusion in the binary logistic regression

model since more stringent significance levels can lead to the exclusion of potentially useful predictor variables [10, 248-250]. Multicollinearity between independent categorical variables was assessed using the phi coefficient [251]. When two variables had a phi coefficient ≥0.30, the model was trialled with each variable independently, and the variable with higher predictive ability was entered into the final model. Variables retained in the final model were used to compute the PADR-EC score. A score of 1 was assigned to variables with an odds ratio (OR) between 1.00 and 1.49; a score of 2 to those with an OR between 1.5 and 2.49; a score of 3 to those with an OR between 2.5 and 3.49; a score of 4 to those with an OR between 3.5 and 4.49 and a score of 5 to those with an OR between 4.5 and 5.49. The PADR-EC score was computed based on the sum of scores of individual variables. Receiver operator characteristic (ROC) curves were constructed, and area under the curve (AUC) calculated to determine the predictive ability of the PADR-EC score. Analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, Illinois).

4.4.5. Validation study

In order to validate the PADR-EC score developed in the RHH sample (derivation stage), it was applied in a separate cohort of adults admitted to medical wards of the Launceston General Hospital (LGH). The LGH is the largest acute care facility and teaching hospital in the northern region of Tasmania. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (Appendix 1), and the study participants provided their written informed consent to participate in the study (Appendix 2). Patients admitted to the LGH during the study period (September to December 2015) were enrolled according to the criteria discussed above. As before, data for all variables were

recorded for each patient, along with details of any suspected ADR-related admission. To evaluate the predictive ability of the PADR-EC score, ROC curves were constructed, and AUC calculated.

4.5. Results

4.5.1. Derivation of the PADR-EC score

Over the 12-month study period, there were 5027 acute unplanned medical admissions in patients aged ≥65 years at the RHH. Of the 1271 (25%) patients screened during the study period, 503 (39.6%) were excluded either due to their unwillingness to consent (130 patients), or an inability to participate due to the severity of their medical condition, hearing impairment or low vision (373 patients). In total, 768 patients were included in the RHH cohort for final analysis. The characteristics of the study populations at the RHH and LGH are summarised in Table 9.

Table 9. Characteristics of the study populations in derivation and validation cohort

Characteristics	Derivation stage (n = 768)	Validation stage (n = 240)
Age in years (mean ± SD)	80.1 ± 7.7	79.6 ± 7.6
Gender (n, %), Female	401 (52.2)	137 (57.1)
Number of medications before hospital admission (mean ± SD)	10.8 ± 5.2	9.9 ± 4.8
Number of comorbidities (mean ± SD)	5.5 ± 2.4	6.0 ± 2.5
Living status (n, %)		
Alone	308 (40.1)	101 (42.1)
With family or friends	433 (56.4)	135 (56.3)
Nursing home	27 (3.5)	4 (1.7)
Comorbidities (n, %)		
Dementia	54 (6.4)	15 (6.3)
Heart failure	136 (16.2)	52 (21.7)
Renal failure	406 (48.4)	125 (52.1)
Cerebrovascular disease	141 (16.8)	37 (15.4)
Diabetes	236 (28.1)	69 (28.8)
Chronic obstructive pulmonary disease	208 (24.8)	89 (37.1)
Cancer	179 (21.3)	67 (27.9)
Anaemia	327 (39)	116 (48.3)
Liver disease	22 (2.6)	11 (4.6)
Depression	94 (11.2)	35 (14.6)
Hyperlipidaemia	240 (28.6)	74 (30.8)
Ischaemic heart disease	160 (19.1)	55 (22.9)
Vascular disease	309 (36.8)	90 (37.5)

Abbreviation: SD, standard deviation.

There was a consensus between the two expert reviewers in the majority of cases and, overall, 115 patients (15.0%) were judged as being admitted due to ADRs. There were 17 doubtful cases that were not classified as ADR-related admissions and were added to the control group (n = 653). There were nine (5.8%) definite and 106 (69.3%) probable ADRs based on the Naranjo algorithm. Most of the ADR-related hospitalisations were considered preventable (106, 92.2%) and all ADRs were classified as Type A reactions except one which was considered as a Type B reaction. As seen in Table 10, univariate analysis identified that PIMs (anticholinergics, antiarrhythmics, benzodiazepines), PIMs use in dementia or cognitive impairment, hospital admission in the preceding month, hospital admission in the preceding three months, drug changes in the preceding three months, nine or more regular medications, seven or more comorbidities, renal failure, dementia, heart failure, anaemia, vascular disease, Charlson comorbidity score ≥6, use of alcohol and age ≥85 years were associated with an increased risk of ADR-related hospital admission ($P \leq 0.20$). Specific drug classes contributing to the risk of ADR-related admission included antihypertensives (1–2, ≥3), angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers, drugs of narrow therapeutic index (digoxin, amiodarone, theophylline, phenytoin, carbamazepine and sodium valproate), psycholeptics, benzodiazepines, tricyclic antidepressants, diuretics and tricyclic antidepressants or psycholeptics. The antihypertensives included α_2-adrenergic agonists, α_1-adrenoreceptor antagonists, β-blockers, calcium channel blockers, diuretics, agents acting on the renin-angiotensin system and vasodilators. Fixed-dose antihypertensive combination therapy, including triple therapy, was used in 12% (n = 95) of patients. The PIMs (anticholinergics) included antihistamines (chlorpheniramine

and promethazine), antispasmodics (hyoscyamine products and atropine products) and tertiary tricyclic antidepressants (amitriptyline, imipramine, and doxepin >6 mg/day).

Table 10. Characteristics of patients experiencing adverse drug reaction-related and non-adverse drug reaction-related hospital admissions at the Royal Hobart Hospital (n=768)

Variable	Number (%)	Number (%)	P Value
	No ADR (n = 653)	**ADR (n = 115)**	
Age (years)			
65–84	454 (69.5)	70 (60.9)	0.07*
≥85	199 (30.5)	45 (39.1)	
Gender			
Male	316 (48.4)	51 (44.3)	0.42
Female	337 (51.6)	64 (55.7)	
Drug-related variables			
Use of OTC medications	275 (42.1)	45 (39.1)	0.55
Use of herbal medications	156 (23.9)	24 (20.9)	0.48
Drug changes in the preceding 3 months	304 (46.6)	70 (60.9)	0.01*
Number of medications			
0–8	245 (37.5)	32 (27.8)	0.05*
≥9	408 (62.5)	83 (72.2)	
Inappropriate medications (Therapeutic category/drug)			
Anticholinergics	57 (8.7)	21 (18.3)	0.002*
Benzodiazepines	128 (19.6)	29 (25.2)	0.17*
Antiarrhythmics	18 (2.8)	8 (7)	0.04*
Digoxin	10 (1.5)	2 (1.7)	0.70
Metoclopramide	14 (2.1)	4 (3.5)	0.33
Inappropriate medications (Disease)			

Variable	Number (%)	Number (%)	P Value
Heart failure	10 (1.5)	1 (0.9)	1.00
Dementia or cognitive impairment	14 (2.1)	8 (7)	0.01*
Disease-related variables			
Charlson Comorbidity Index			
0–5	344 (52.7)	52 (45.2)	0.14*
≥ 6	309 (47.3)	63 (54.8)	
Cerebrovascular diseases	117 (17.9)	24 (20.9)	0.45
≥7 Comorbidities	206 (31.5)	51 (44.3)	0.01*
Diabetes	200 (30.6)	36 (31.3)	0.89
Anaemia	270 (41.3)	57 (49.6)	0.10*
Depression	81 (12.4)	13 (11.3)	0.74
Acute cognitive impairment	41 (6.3)	5 (4.3)	0.42
Dementia	42 (6.4)	12 (10.4)	0.12*
*Renal failure***	323 (49.7)	83 (72.8)	<0.001*
Liver disease	18 (2.8)	4 (3.5)	0.56
Heart failure	108 (16.5)	28 (24.3)	0.04*
COPD	176 (27)	32 (27.8)	0.85
Cancer	156 (23.9)	23 (20)	0.36
Hyperlipidaemia	204 (31.2)	36 (31.3)	0.99
Ischaemic heart disease	133 (20.4)	27 (23.5)	0.45
Vascular disease	254 (38.9)	55 (47.8)	0.07*
Variables related to drug classes			
Drugs of narrow therapeutic index	158 (24.2)	38 (33)	0.05*
Antithrombotics	444 (68)	85 (73.9)	0.21
Antihypertensives			
0	131 (20.1)	6 (5.2)	
1–2	328 (50.2)	51 (44.3)	<0.001*
≥3	194 (29.7)	58 (50.4)	

Variable	Number (%)	Number (%)	P Value
ACEIs or ARBs	357 (54.7)	77 (67)	0.01*
Calcium channel blockers	172 (26.3)	34 (29.6)	0.47
Cardiac glycosides	69 (10.6)	15 (13)	0.43
β-Blockers	223 (34.2)	52 (45.2)	0.02*
Drugs used in diabetes	156 (23.9)	29 (25.2)	0.76
NSAIDs	27 (4.1)	6 (5.2)	0.60
Opioids	199 (30.5)	41 (35.7)	0.27
Psycholeptics	158 (24.2)	36 (31.3)	0.11*
Antipsychotics	37 (5.7)	9 (7.8)	0.37
Benzodiazepines	137 (21)	32 (27.8)	0.10*
Tricyclic antidepressants	57 (8.7)	15 (13)	0.14*
Tricyclic antidepressants or psycholeptics	197 (30.2)	46 (40)	0.04*
Antiplatelets	320 (49)	61 (53)	0.42
Diuretics	309 (47.3)	80 (69.6)	<0.001*
Antibacterials	94 (14.4)	14 (12.2)	0.53
Anticoagulants	140 (21.4)	30 (26.1)	0.27
Other variables			
Admission in preceding month	159 (24.3)	38 (33)	0.05*
Admission in preceding 3 months	269 (41.2)	55 (47.8)	0.18*
Use of dosage administration aid	259 (39.7)	45 (39.1)	0.91
*Use of generics****	345 (60.5)	62 (62.6)	0.69
Use of alcohol	241 (36.9)	35 (30.4)	0.18*
Smokers	72 (11)	9 (7.8)	0.30
*Presence of ADR within 3 months*****	106 (16.5)	22 (20.2)	0.35
*Previous ADR***	389 (59.8)	65 (57)	0.57
Regular pharmacy visits	582 (89.1)	105 (91.3)	0.48
HMR in the preceding 3 months	41 (6.3)	5 (4.3)	0.42

Variable	Number (%)	Number (%)	P Value
Assistance required with ≥1 activity of daily living	433 (66.3)	83 (72.2)	0.22
Albumin <3.5 g/dL	293 (44.9)	54 (47)	0.68
Falls	38 (5.8)	6 (5.2)	0.80

Abbreviations: ADR, adverse drug reaction; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; HMR, Home Medicines Review; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over-the-counter.

* P value ≤0.20.

** 4 participants had missing values.

*** 99 participants had missing values.

**** 17 participants had missing values.

When variables were excluded due to multicollinearity, the variables retained in the model were hospital admission in the preceding month, drug changes in the preceding three months, seven or more comorbidities, renal failure, dementia, drugs of narrow therapeutic index, antihypertensives (1–2, ≥3), anaemia, PIMs (anticholinergics), psycholeptics, age ≥85 years and use of alcohol. Binary logistic regression retained drug changes in the preceding three months, renal failure, dementia, antihypertensives (1–2, ≥3), and PIMs (anticholinergics) as significant predictors of ADR-related hospital admission (Table 11). These variables were assigned scores based on their respective ORs (Table 12).

Table 11. Binary logistic regression of factors associated with adverse drug reaction-related hospital admission in the derivation study at the Royal Hobart Hospital (n=768)

Variable	Adjusted OR (95% CI)	P value
Age ≥85 years	1.33 (0.86–2.06)	0.20
Drug changes in the preceding three months	1.54 (1.00–2.37)	0.05
Anaemia	1.08 (0.70–1.65)	0.74
Renal failure	1.97 (1.22–3.17)	0.01
Drugs of narrow therapeutic index	1.15 (0.73–1.81)	0.55
Dementia	2.44 (1.17–5.10)	0.02
Admission in preceding month	1.31 (0.82–2.07)	0.26
Number of comorbidities ≥7	1.07 (0.69–1.66)	0.76
Number of antihypertensives		
1–2	3.00 (1.22–7.38)	0.02
≥3	4.75 (1.89–11.93)	0.001
Anticholinergics	2.09 (1.16–3.75)	0.01
Psycholeptics	1.24 (0.78–1.98)	0.36
Use of alcohol	0.80 (0.51–1.25)	0.32

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 12. Variables included in the risk score

Variable	OR (95% CI)	Points
Drug changes in the preceding three months	1.54 (1.00–2.37)	2
Renal failure	1.97 (1.22–3.17)	2
Dementia	2.44 (1.17–5.10)	2
Number of antihypertensives		
1–2	3.00 (1.22–7.38)	3
≥3	4.75 (1.89–11.93)	5
Anticholinergics	2.09 (1.16–3.75)	2

Abbreviations: CI, confidence interval; OR, odds ratio.

Drug changes in the preceding three months, renal failure, dementia and PIMs (anticholinergics) were scored at two points, and antihypertensives received a score of three points (1–2 antihypertensive agents) or five points (≥3 antihypertensives). The range of scores was from zero to 11, with a median of five (IQR 5). The area under the ROC curve, which assesses the ability of the risk score to predict ADR-related hospitalisation in the whole population, was 0.70 (95% CI 0.65–0.75) (Appendix 10). A score cut off at six provided a good balance between sensitivity (72.2%) and specificity (58.0%). The risk of patients having an ADR-related hospitalisation was more than three times higher in those who scored ≥6 compared to those who scored <6 (OR 3.59 [95% CI 2.32–5.55]).

4.5.2. Validation study

Over the study period of 4 months, 518 patients were screened at the LGH. Of these, 123 patients were excluded due to their unwillingness to consent and 155 patients could not be recruited due to the severity of their medical condition. In total, 240 patients were included in the LGH cohort for the validation of the PADR-EC score. Definite (2, 5.2%)

and probable (28, 73.7%) ADR-related hospital admissions were observed in 30 patients (12.5%) in this sample. The patients' characteristics are summarised in Table 9.

The majority of the ADR-related hospitalisations were considered preventable (24, 80%). When the PADR-EC score was applied to the LGH data set, the AUC was 0.67 (95% CI 0.56–0.78) (Appendix 10). A score cut off at six provided a good balance between sensitivity (63%) and specificity (63%). In the LGH data set, patients who scored ≥6 had almost three times the risk of ADR-related hospitalisation compared to those scoring <6 (OR 2.92 [95% CI 1.32–6.46]). The percentage increase of ADR-related hospitalisation with respect to the cut-off score ≥6 in both the RHH and LGH data set is outlined in Figure 3.

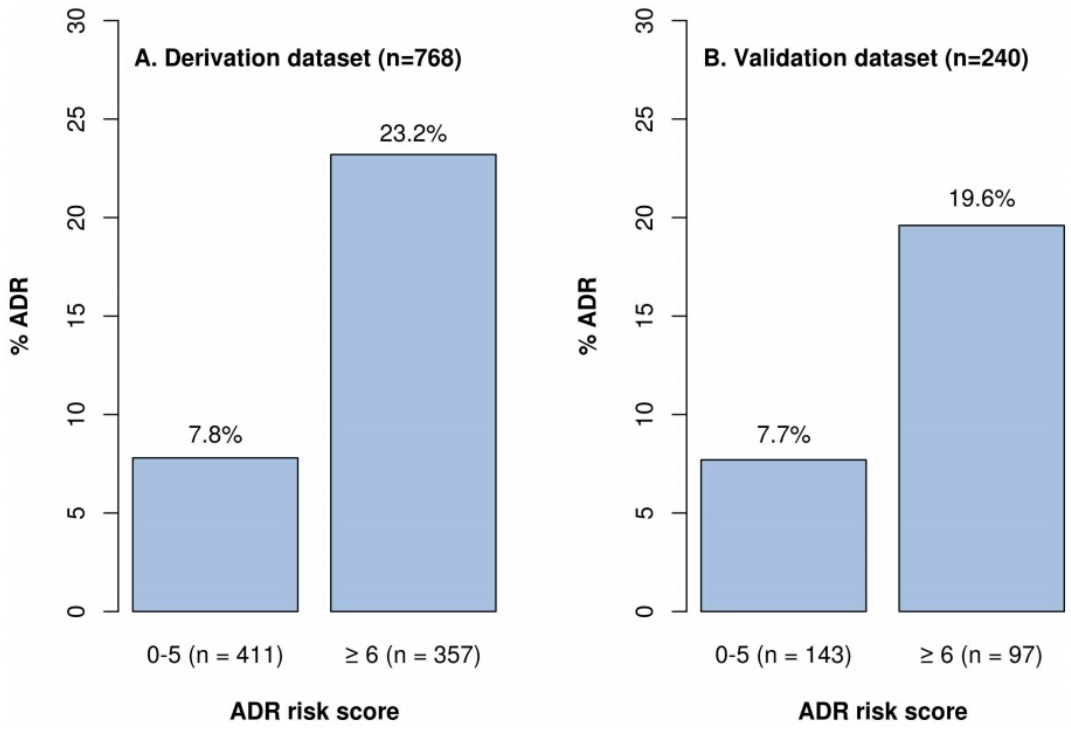

Figure 3. Adverse drug reaction rate according to risk score

(A) The adverse drug reaction rate at cut off score at 6 in the derivation dataset at the Royal Hobart Hospital. (B) The adverse drug reaction rate at cut off score at 6 in the validation dataset at the Launceston General Hospital.

4.6. Discussion

We developed and validated a simple and robust approach to identifying community-dwelling elderly patients at risk of hospitalisation due to ADRs. To our knowledge, this is the first study to develop such a score. This score has the potential to assist healthcare practitioners to identify those elderly patients for whom intervention may reduce the risk of ADRs and subsequent hospitalisation. In addition, patients could be stratified at hospital discharge according to their risk of subsequent admission of an ADR, and appropriate medication management services provided accordingly post-discharge.

The variables we identified as independent predictors of ADRs in the elderly have been described in previous studies [175, 252-254]. Drug changes in the preceding three months were found to predict ADR-related admission in the present study. Changes in medications such as using a different dose, discontinuing therapies, and taking new drugs were observed in the majority of elderly patients after hospital discharge in a follow-up study [246] and clinically significant changes to medicines or treatment plans within the last 3 months were found to be a risk factor for medication-related problems [252, 255]. ADRs attributed to medication changes occurred in 20% of patients during transfer from hospital and nursing home in a study conducted in United States of America [256]. Renal failure was found to be another significant predictor of ADR-related admission in the present study. The relation between renal insufficiency and ADRs is well documented in the literature [257, 258]. Impaired renal function (OR 2.6, 95% CI 1.6–4.2) was found to be a major determinant of preventable medication-related hospital admission in a prospective multicentre study [208]. Renal failure was also found to be a predictor of ADRs in the GerontoNet ADR score study (OR 1.2, 95% CI 0.9–1.5) as well as in a prospective study of elderly individuals who presented to an emergency department (OR

1.5, 95% CI 1.1–2.2) [9, 190]. In the present study, we found elderly patients with renal failure were twice as likely to be hospitalised due to ADRs. The presence of dementia was identified as another independent predictor of ADR-related hospitalisation. The prevalence of ADRs in elderly patients with dementia was 5.0% in another study; half of the ADRs were due to use of psychotropic and anti-dementia drugs [259]. Drug-related problems appeared to be responsible for the majority of hospitalisations among old people with dementia, and the most common drug-related problem was an ADR (18.7%) in a recent study [217].

PIMs are significantly associated with ADRs and subsequent hospital admission [238]. Inappropriate medications were associated with a two-fold increased risk of an ADR in the elderly in a prospective study [167]. Among the PIMs, use of anticholinergics was found to be the predictor of ADR-related hospital admission in the present study. The prevalence of exposure to anticholinergic medicines in the elderly has ranged from 22.8% to 55.9% [260]. The use of drugs with anticholinergic adverse effects is often inappropriate in older patients aged ≥65 years [261]. Many age-related and disease-related conditions may predispose older patients to ADRs related to anticholinergic drugs [262]. These drugs have many effects in the elderly, ranging from dry mouth and constipation to confusion, delirium and severe cognitive impairment [263]. Another important predictor of ADR-related admission in the present study was the use of multiple antihypertensives. Approximately 70% of patients with hypertension require two or more drugs to achieve their target blood pressure [264]. The use of multiple antihypertensives in elderly patients is a frequent cause of hospital admission [265]. Antihypertensives were found to be one of the most frequently implicated drugs in causing ADRs, and the risk is higher with combination therapy and in patients receiving multiple antihypertensive drugs

[266-268]. In a community-based randomised open label trial [269] there was a significant increase in dizziness reported with combination antihypertensive therapy. The prevalence of orthostatic hypotension has been reported to be between 35% and 65% for the elderly and is mainly associated with the use of antihypertensive medications [231, 270, 271].

This study found that almost 15% of admissions in the elderly were due to ADRs. Meta-analysis of observational studies in the elderly reported a similarly high rate (16.6%) of ADR-related hospitalisation [101]. The PADR-EC score has a predictive ability of 70% to discriminate patients who are at high risk of ADR-related hospitalisation and those who are not. The subsequent validation study found a predictive ability of 67%. The sensitivity of the score was 72% in the derivation cohort, which indicates the ability of the score to correctly classify a patient as a victim of preventable ADR-related admission. Importantly, the expert reviewers also identified that the majority of ADR-related admissions were preventable. The predictive ability of the risk score could, therefore, be utilised to identify ADRs which may be prevented by monitoring of patients' drug therapy, addressing inappropriate dosing, aiding patient compliance with therapy and managing drug interactions to avoid subsequent admission. To our knowledge, there is no previously developed ADR prediction tool for use in primary care to which to compare the present study findings; however, the score performed comparably to validated ADR prediction tools used to predict ADR risk in hospitalised patients, such as those developed by Onder et al. (predictive ability of 71%) [9] and Tangiisuran et al. (74%) [10]. While there are tools available to predict the risk of emergency admission to hospital [272-274], our tool was developed to focus specifically on the risk

hospitalisation due to an ADR to enable primary health care professionals to better direct medication management services to prevent ADRs.

The PADR-EC score consists of five clinical variables that are easy to apply and practical to assess in elderly patients. The development of this tool may assist general practitioners or primary care physicians in identifying older patients who have a high risk of ADRs and subsequent emergency hospital admissions [238]. This is particularly important considering that it may be challenging for healthcare practitioners to easily identify patients who are at risk of hospitalisation due to ADRs, partly due to significant time pressures in office-based practice [171]. The PADR-EC score could potentially be integrated into prescribing software to alert primary care physicians to their patients' risk of ADRs and prompt appropriate preventive measures. Such preventive measures may include medication review, avoiding use of PIMs, computer-based prescribing systems and comprehensive geriatric assessment [3], as well as deprescribing (withdrawal of an inappropriate medication) [275] and avoiding unnecessary polypharmacy when drugs are no longer efficacious or beneficial, or when safer alternatives exist [276]. The PADR-EC score could also be applied at hospital discharge to identify older patients who are at higher risk of admission for ADRs to facilitate post-discharge medication management review services and/or closer monitoring by relevant health professionals to prevent subsequent hospitalisation. Thus, application of PADR-EC score could potentially play a role in reducing the risk of ADR-related hospitalisations in the elderly.

Limitations include the score's specificity of 58%, resulting in a chance of incorrectly labelling patients as 'having an ADR risk' who may not be at risk (false positives). The validation sample had almost equal or slightly less discriminatory power compared to the derivation sample, suggesting that further refinement and testing of the

PADR-EC score is required before implementing the score in clinical practice. The time restraints did not allow us to validate the tool further in a community setting to follow the patients in primary care to observe an ADR related hospital admission outcome versus other disease related outcomes. However, the variables used to derive the score only used patient information before hospital admission and all the patients recruited in the study were primary care patients. There were inherent limitations in assessing the predictor 'drug changes in the preceding three months', as this could have potentially been influenced by incomplete records. We minimised this issue by interviewing the patient/relatives about their medication usage, including recent changes to drug therapy, and comprehensively reviewing medical records and, importantly, medication reconciliation reports from clinical pharmacists. Some of the variables arose from patient interviews and thus could be a subject to recall bias; this was limited by conducting interviews in the presence of family members. We could not recruit some patients due to difficulty in getting the consent mainly due to their severity of disease. Thus, obtaining consent was the limiting step, and a retrospective study could have included these additional patients, although such a study would lose the ability to obtain information through interview. The degree of generalisability of the proposed model is restrained by convenience sampling, however the large sample size used in the study may have reduced the sampling error and hence, may not have affected the applicability of the proposed model. We cannot assess the time frame for ADR occurrence after identifying patients at risk. Hence, further studies are required to address this issue in order to predict ADRs and subsequent admission in a timely fashion. Further investigation is needed to determine the absolute risk for people identified as being at high-risk of ADRs using this score, and

whether interventions in these patients by health care professionals are able to reduce this risk.

4.7. Conclusion

We propose a simple, efficient and practical tool to identify elderly patients living in the community who are at increased risk of ADR-related hospitalisation. The PADR-EC score was developed and externally validated reasonably in a cohort of elderly subjects admitted to two participating centres. It has the potential to be easily used, mainly by primary care physicians or perhaps other health care professionals (e.g. pharmacists and nurses) to identify elderly patients vulnerable to ADRs, and target interventions to prevent subsequent hospitalisation. Even though further refinement and testing of this tool is necessary before implementing the score in clinical practice, this tool could provide a useful starting point to predict risk for ADR-related hospitalisation in the elderly. Further studies are required to assess the clinical utility of this tool in different settings and populations.

CHAPTER FIVE

5. Repeat Adverse Drug Reactions-Related Hospital Admissions in Elderly Australians: A Retrospective Study at the Royal Hobart Hospital

5.1. Preface

Chapter 4 described the development and validation of a simple and practical score to identify elderly patients who are at an increased risk of preventable ADR-related hospital admission. The study also concluded that the score could potentially be applied at hospital discharge to stratify elderly patients according to their risk of subsequent ADR-related hospital admission. This chapter presents the results of a study that investigated the utility of the ADR score in this setting.

Submitted manuscript:

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5.2. Abstract

Introduction: Adverse drug reactions (ADRs) are a major cause of hospital admissions in older individuals, with the majority potentially preventable. Despite the apparent magnitude of this problem, little is known about rates of repeat admission to hospital due to ADRs.

Objectives*:* To investigate the occurrence of repeat ADR-related hospital admissions in elderly patients within 12 months of an ADR-related admission to a medical ward and to investigate whether a validated ADR score could be useful in identifying patients at higher risk of a repeat ADR-related hospitalisation.

Methods: This retrospective study followed elderly participants who were hospitalised with an ADR from our earlier study (the PADR-EC [Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients] study) to identify repeat ADR-related hospital admissions within 12-months of discharge. The PADR-EC score is the sum of points assigned to five significant predictors of ADR-related hospitalisation - antihypertensive use, renal failure, dementia, anticholinergic use and drug changes in the preceding three months. The causality, preventability, and severity of each ADR-related repeat admission within the 12-month follow up period were assessed.

Results: ADR-related repeat admissions occurred after 13.4% (n=15) of 112 ADR-related index admissions. Patients with a repeat ADR-related admission had significantly higher PADR-EC scores at discharge of their index admission (median PADR-EC score 7, IQR 7-9) than patients who were not readmitted (median PADR-EC score 7, IQR 5-7,

P=0.034). Most (73.3%) ADR-related repeat admissions were considered ‘preventable’. ADR severity was ‘moderate’ in all cases. Renal disorders (44.4%) represented the most common ADRs, and the most frequently implicated drug classes were diuretics (44.8%). All ADR-related repeat admissions were found to be ‘probable’.

Conclusions: One in eight elderly patients hospitalised due to an ADR had a repeat admission for an ADR within 12 months of discharge. The PADR-EC score could potentially be used at hospital discharge to prioritise patients for interventions to prevent subsequent ADR-related hospital admission.

Key Points

- One in eight elderly patients hospitalised due to an adverse drug reaction (ADR) had a repeat admission for an ADR within 12 months of discharge.
- A PADR-EC (Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients) score ≥6 at discharge could be used as a trigger for intervention to reduce the risk of subsequent ADR-related hospitalisation.

5.3. Introduction

Adverse drug reactions (ADRs) are an important cause of hospitalisation in the elderly [238]. A recent study estimated that almost one in five unplanned overnight hospital admissions to medical wards in elderly Australian patients were related to ADRs [277] . It is estimated that more than half of these admissions are preventable [7]. ADRs which result in hospitalisation in patients with a history of ADR-related hospitalisation, or 'repeat ADRs', are increasingly common and an important contributor to the burden of ADRs [278-280]. For example, Zhang et al. conducted a population-based longitudinal study (1980-2003) in Australia and found that repeat ADR-related hospitalisations had increased faster than first-time ADRs in the elderly since 1980 and were responsible for 30.3% of all ADR-related admissions in 2003 [73].

The authors recently developed a validated ADR score (the PADR-EC [Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients] score) to identify community-dwelling elderly patients at risk of hospitalization due to preventable ADRs [214]. We concluded that the score could potentially be useful to stratify elderly patients at hospital discharge according to their risk of subsequent admission due to an ADR, and guide the provision of post-discharge medication management services. ADRs and subsequent ADR-related hospital admissions in the high-risk older population are of equally significant concern and more studies in this area are required to investigate methods to reduce the risk of repeat ADRs. The present study aimed to compare the PADR-EC score at the point of discharge in patients with and without repeat ADR-related admissions within 12 months of their index ADR-related hospital admission to identify whether a high PADR-EC score was associated with a higher risk of hospitalisation for repeat ADRs.

5.4. Methods

We used the data collected as part of a prospective cross-sectional study on ADR-related hospital admissions in elderly patients (aged ≥65 years), conducted at the Royal Hobart Hospital (RHH), Tasmania, Australia. This published study described the derivation of an ADR prediction score (the PADR-EC score) using data from the RHH (March 2014 to March 2015) and further validation of the score at a second hospital [214]. In this study, ADR-related admissions were identified from detailed review of medical records and patient interviews, followed by consensus agreement between two expert clinical pharmacists. The PADR-EC score assigns points to five significant predictors of ADR-related hospitalisation: (i) antihypertensive use (3 or 5 points if 1-2 or ≥3 antihypertensives, respectively), (ii) renal failure (estimated glomerular filtration rate [eGFR] <60mL/min/1.73m^2) (2 points), (iii) dementia (2 points), (iv) inappropriate anticholinergic use (2 points), and (v) drug changes in the preceding three months (2 points). These points are summed to produce the final score, with the risk of ADR-related hospitalisation more than three times higher in those with a score ≥6.

For this analysis, we collected data from the digital medical records (DMR) of elderly participants in the PADR-EC study who experienced a subsequent admission due to an ADR. The RHH implemented a DMR in 2006 with the aim of allowing improved access to all patient histories for authorised staff and improve the ability of staff to access all hospital clinical information databases via a single electronic link [281].The medication history taking and reconciliation by clinical pharmacists is standard practice at the RHH and this, together with the clinical notes relating to the hospital admission, are all available electronically via the DMR enabling comprehensive retrospective review.

Patients were included in the study if they were admitted due to an ADR within 12 months of discharge from their initial ADR-related admission. The reasons for hospitalisation were multifactorial in many cases, and hence if there were other reasons for repeat admission as well as the ADR, the contribution of an ADR to hospital admission or if ADRs were one of the reasons for hospital admission were considered [96, 282]. We used a consensus method to identify and categorise ADR-related repeat hospital admissions. Patients were classified as having an ADR-related admission by the primary clinical pharmacist researcher if the reason for admission was consistent with the known ADRs of the drug and if other reasons were excluded after suitable investigations. All potential repeat ADR-related admissions were assessed by another senior clinical pharmacist, and a consensus decision was reached if there was a discrepancy between the two pharmacists' assessments. The consensus decision was based on a further discussion and comprehensive review of the potential ADR cases again and exclusion of any doubtful cases. An ADR was defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [283]. The causality of the relation between drug use and ADR-related hospitalisation was assessed using the Naranjo algorithm (Appendix 8) [179]. ADRs were classified as definite (score from 9 to 12), probable (score from 5 to 8), possible (score from 1 to 4), or doubtful (score from 0 to -2), with only definite and probable ADRs being considered for this study. The modified Schumock and Thornton criteria were used to evaluate the preventability of the ADR (preventable or not preventable) [214, 221]. Severity of ADRs was assessed using the Hartwig *et al.* scale (Appendix 9) [222]. ADRs were also classified as Type A and Type B reactions based on the criteria of Rawlins and Thompson [223], and also whether

they were due to any drug-drug interactions (DDIs) as evaluated using the UpToDate database (Lexi-Interact™ Online) [216]. The outcome of the ADR-related admission was categorised as recovery (i.e., patients were clinically stable at discharge), death or unknown. Medications taken prior to admission were defined according to the Anatomical Therapeutic and Chemical classification system [219]. Clinical diagnosis and comorbidities were encoded according to the International Classification of Primary Care, 2nd edition [240]. Renal failure was defined as an eGFR of less than 60 mL/min/1.73m^2 or as documented in the medical records [242, 243]. We considered acute kidney injury as an ADR if there was an acute reduction in renal function from baseline of 30% or more [284]. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (Appendix 1).

5.4.1. Statistical Analysis

The results were presented as either median and interquartile range (IQR) or frequencies and percentages. We used the Mann-Whitney U test to compare the PADR-EC scores at discharge of patients' index admissions. A P value <0.05 was considered as being significant. Statistical analysis was performed with SPSS version 20.0 (SPSS Inc, Chicago, Illinois).

5.5. Results

In the prospective PADR-EC study at the RHH, 115 patients (15.0%) were judged as being admitted due to ADRs [214]. Of these, three patients died during their index admission, leaving 112 patients included in the analysis of ADR-related repeat admissions. Repeat ADR-related admissions occurred within 12 months of discharge in

13.4% (n=15) of these 112 ADR-related index admissions. Of these, eight (53.3%) patients had a repeat admission for ADRs within three months of their index admission, two (13.3%) within 3 to 6 months and five (33.3%) within 6 to 12 months. Twelve (80%) patients were calculated to have a PADR-EC score ≥6 at hospital discharge after their index admission (Table 13).

Table 13. PADR-EC scores at discharge of index admissions of patients who were readmitted due to adverse drug reactions (n=18)

PADR-EC score	Number of patients (%)
2	1 (5.6)
5	2 (11.1)
6	1 (5.6)
7	8 (44.4)
9	5 (27.8)
11	1 (5.6)

Abbreviation: PADR-EC, Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients.

Patients with a repeat ADR-related admission had significantly higher PADR-EC scores at discharge of their index admission (median PADR-EC score 7, IQR 7-9) than patients who were not readmitted with ADRs (median PADR-EC score 7, IQR 5-7, P=0.034). A box plot of PADR-EC scores by readmission status is outlined in Appendix 11. Eleven of the repeat admissions due to ADRs (73.3%) were considered 'preventable' based on Schumock and Thornton's criteria. ADR severity was rated 'moderate' in all ADR-related repeat admissions. Using the Naranjo algorithm, all ADR-related repeat

admissions were found to be probable. For most admissions (n=14, 93.3%), the ADR resolved and the patient recovered; in one case (6.6%), the outcome was unknown due to the patient's transfer to another hospital. In nine cases (60.0%), the patient was admitted with the ADR caused by the same drug/drug classes as in the index admission and in four cases (26.7%), the same ADRs contributed to both admissions. In five cases (33.3%), re-prescription of discontinued medications from the index admission contributed to repeat admission. The nature of the ADRs in the index and repeat admissions are outlined in in Table 14.

Table 14. The nature of the adverse drug reactions in the index and repeat admissions

	Index admission ADR			Repeat admission ADR			
No.	**ADR**	**Drugs involved**	**Reasons of preventability**	**ADR**	**Drugs involved**	**Reasons of preventability**	**Comments**
1	Hypotension, dizziness, syncope	Amlodipine, candesartan, furosemide, glyceryl trinitrate, metoprolol	Drug-drug interactions	Acute kidney injury	Candesartan	Inappropriate dosing	Antihypertensives caused both admissions.
		Oxazepam	Not preventable		Furosemide	Not preventable	
2	Hypoglycaemia	Sitagliptin, gliclazide	Inappropriate dosing and drug-drug interactions	Hypothyroidism	Amiodarone	Inappropriate dosing	Patient was on amiodarone during the index admission, and amiodarone was not discontinued during the index admission.
3	Rash	Furosemide	History of same previous ADR	Diarrhoea, acute kidney injury	Ethacrynic acid, digoxin	Inappropriate dosing	Diuretics caused both admissions.
					Losartan	Not preventable	

No.	ADR	Drugs involved	Reasons of preventability	ADR	Drugs involved	Reasons of preventability	Comments
4	Haemorrhage	Clopidogrel	Drug-drug interactions	Hypoglycaemia	Insulin, metformin	Drug-drug interactions	-
5	Acute kidney injury	Irbesartan	Not preventable	Hypotension, syncope	Irbesartan, propranolol	Not preventable	Antihypertensives caused both admissions.
6	Nausea, vomiting	Theophylline	Inappropriate dosing	Hypotension	Furosemide, ramipril	Drug-drug interactions	-
7	Hyponatremia	Spironolactone	Inappropriate dosing	Hyperkalaemia	Spironolactone	Not preventable	Diuretics caused both admissions.
		Furosemide	Not preventable				
8	Acute kidney injury	Furosemide, ramipril	Drug-drug interactions	Acute kidney injury	Furosemide, ramipril	Drug-drug interactions	Diuretics and ACEIs caused both admissions. Repeat ADR occurred after re-initiation of diuretics and

No.	ADR	Drugs involved	Reasons of preventability	ADR	Drugs involved	Reasons of preventability	Comments
							ACEIs that were withheld in the index admission.
9	Acute kidney injury	Furosemide, allopurinol	Drug-drug interactions	Acute kidney injury	Spironolactone	Inappropriate dosing	Diuretics caused both admissions. Repeat ADR occurred after re-initiation of diuretics that were withheld in the index admission.
10	Acute kidney injury	Ramipril, furosemide	Drug-drug interactions	Acute kidney injury	Furosemide, ramipril	Drug-drug interactions	Diuretics and ACEIs caused both admissions. Repeat ADR occurred after re-initiation of diuretics and ACEIs that were withheld in the index admission.
11	Urinary retention, hyponatremia	Fluvoxamine	Not preventable	Severe nausea	Trimethoprim	Not preventable	-

No.	ADR	Drugs involved	Reasons of preventability	ADR	Drugs involved	Reasons of preventability	Comments
12	Bradycardia	Metoprolol	Not preventable	Acute kidney injury, hyperkalaemia	Candesartan, spironolactone	Inappropriate dosing and drug-drug interactions	-
					Furosemide	Not preventable	
13	Acute kidney injury, hyponatremia	Spironolactone	Inappropriate dosing	Acute kidney injury	Spironolactone	Inappropriate dosing	Diuretics and ARBs caused both admissions. Repeat ADR occurred after re-initiation of diuretics and ARBs that were withheld in the index admission.
		Furosemide, candesartan	Not preventable		Candesartan, furosemide	Not preventable	

No.	ADR	Drugs involved	Reasons of preventability	ADR	Drugs involved	Reasons of preventability	Comments
14	Acute kidney injury, hyperkalaemia, orthostatic hypotension	Spironolactone, perindopril, furosemide, prazosin	Inappropriate drug for the patient's condition and drug-drug interactions	Increased lactate levels	Metformin	Inappropriate dosing	Patient's eGFR was 16 mL/min and was on metformin 2 g/day during the index admission. Repeat ADR occurred after restarting of metformin, which was withheld in the index admission.
		Amitriptyline	Not preventable				
15	Bradycardia, hyperkalaemia	Candesartan, spironolactone	Drug-drug interactions	Acute kidney injury	Candesartan, furosemide	Not preventable	Diuretics and ARBs caused both admissions. Repeat ADR occurred after re-initiation of diuretics and ARBs that were withheld in the index admission.
		Bisoprolol	Not preventable				

Abbreviations: ADR, adverse drug reaction; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate.

Twelve patients (80.0%) had a single ADR, and three (20.0%) had two ADRs. In four (26.7%) cases the ADRs were caused by a single drug, and in 11 (73.3%) cases, the ADRs were caused by a combination of drugs. DDIs were potentially involved in 33.3% (n=5) of the cases. Overall, 18 ADRs caused by 29 drugs contributed to all repeat admissions. All ADRs were classified as Type A reactions. Renal disorders (8, 44.4%) represented the most common manifestation of ADRs, followed by endocrine/metabolic disorders (5, 27.8%) (Table 15). The drug classes most frequently causing repeat admission due to ADRs were diuretics (13, 44.8%), renin-angiotensin system inhibitors (9, 31.0%) and drugs used in metabolic disorders (3, 10.3%) (Table 16). The main reasons for the preventable reactions in the repeat ADR-related hospital admissions were inappropriate drug dosing (7, 46.7%) followed by involvement of a DDI (5, 33.3%). The patient wise suspected drugs in the index and repeat ADR-related hospital admissions, and reasons for the preventable ADR in both admissions are also summarised in Table 14.

Table 15. Clinical presentations of repeat adverse drug reaction-related hospitalisation

Type of ADR	n (%)	ADRs causing or contributing to hospital admission (n=18)
Renal	8 (44.4)	Acute kidney injury (8)
Endocrine and metabolic	5 (27.8)	Hypothyroidism (1), hypoglycaemia (1), hyperkalaemia (2), increased lactate levels (1)
Cardiovascular	3 (16.7)	Hypotension (2), syncope (1)
Gastrointestinal	2 (11.1)	Diarrhoea (1), nausea (1)

Abbreviation: ADR, adverse drug reaction.

Table 16. Drug classes contributing to repeat adverse drug reaction-related hospitalisation

Drug class	Frequency (%)	Drugs involved (n=29)
Diuretics	13 (44.8)	Furosemide (8), ethacrynic acid (1), spironolactone (4)
Agents acting on the renin-angiotensin system	9 (31.0)	Candesartan (4), irbesartan (1), losartan (1), ramipril (3)
Drugs used in metabolic disorders	3 (10.3)	Insulin (1), metformin (2)
β-Blocking agents	1 (3.4)	Propranolol (1)
Cardiac glycosides	1 (3.4)	Digoxin (1)
Antiarrhythmic agents	1 (3.4)	Amiodarone (1)
Systemic antibacterial agents	1 (3.4)	Trimethoprim (1)

5.6. Discussion

We found that approximately 13% of patients hospitalised due to an ADR had a repeat admission for ADR within 12 months of discharge from their initial index admission. The PADR-EC score was significantly higher in patients who had a repeat admission for ADRs, and the majority (80.0%) of patients who had a repeat ADR admission had a PADR-EC score ≥6 at hospital discharge after their index admission. These repeat admissions occurred mostly within the first three months after discharge from their initial index admission.

The proportion of ADR-related repeat admissions varies in the literature [278], but a similar rate of 17.7% was found in another Australian study [197]. In our study, 73% of repeat ADRs were considered preventable, and all were Type A reactions

resulting from known pharmacological actions of the implicated agents. In other studies, the preventability varied from 44.4-57.1% [278, 279], though these studies were not focussed on elderly patients. Renal disorders represented the most common manifestation of repeat ADRs, which is also consistent with the literature [279]. In more than half of the patients with repeat ADRs, the repeat ADR was caused by the same drug class/classes as in the index admission. ADRs due to the same drug combination were the suspected cause of repeat admission in half the cases in another study in elderly patients [280].

We comprehensively reviewed the patients' DMR to identify the repeat ADR admissions, which is different from other international studies in which repeat ADRs were identified using International Classification of Diseases codes [73, 197, 278, 280]. However, our study has some limitations. The small number of repeat ADR cases observed in our cohort allowed us to assess repeat ADR-related admissions only descriptively. Additionally, the study was performed in one hospital, and therefore we did not assess repeat ADR admissions to other hospitals. Since this study was a secondary ad hoc analysis of the main PADR-EC study, a power calculation was not done. These limitations might have implications for the extrapolation of the findings and reduce the generalisability of the results to the entire Australian population. However, the characteristics of our patient population, such as age, number of comorbidities, implicated drugs, and common repeat ADRs, were comparable to a similar Australian study in hospitalised elderly populations [73], supporting the generalisability of our findings. The data for patients who died after the index admission were also lacking. These limitations might result in underestimation of the number of repeat ADR cases in our study, and further studies exploring the burden of repeat ADRs including their independent predictors are required to confirm our findings. The difficulty in assessing the

contribution of an ADR to a repeat admission is a limitation of retrospective studies. However, we overcame this limitation by comprehensively reviewing the DMR, as well as the prospective collection of the original PADR-EC study data. Although the median PADR-EC scores were identical, the statistically significant difference is due to the higher readmission scores shown as a higher IQR compared to the non-readmission group. We suggest that the utility and clinical importance of the PADR-EC score should be explored in future studies. This method also did not allow us to determine the predictive ability of the score in this setting. However, the significantly higher PADR-EC score in patients who had a repeat admission for ADRs suggests that a score ≥6, as estimated in the original PADR-EC study, could be used to screen patients who are most vulnerable to repeat ADR-related admissions. We suggest further studies in a large cohort of elderly patients to test the predictive ability of the PADR-EC score.

Strategies to prevent repeat ADR-related hospital admissions are urgently needed in elderly patients. More than half of the repeat ADRs were caused by the same medications as at the index admission, which suggests that monitoring of high-risk medications (e.g., diuretics) in these patients at hospital discharge may not be adequate. The re-prescription of medications discontinued during the index admission was also responsible for some ADR-related repeat admissions. This highlights that transfer of information to primary care physicians or general practitioners (GPs) about drug discontinuation and the reasons for discontinuation is an important communication issue. In another descriptive study, a quarter of the drug treatments withdrawn during hospitalisation because of an ADR were represcribed within six months after discharge, however, the transfer of information to GPs and documentation by GPs were poor [285]. The significantly higher PADR-EC scores observed in the present study in those patients

who had a repeat admission for ADRs suggests that the score could potentially be used at hospital discharge to prioritise patients for interventions to prevent subsequent ADR-related admissions. To our knowledge, this approach has not been used before in the field of assessing repeat ADRs. Dominique et al. studied the impact of interventions on drug-related problem-related readmission rates in older adults and found that an intervention was associated with 39.7% fewer readmissions related to ADRs in the elderly [286], which suggests that a targeted approach may be effective. The score is designed to be simple to use for health professionals, and could easily be incorporated into hospital-based decision support systems to guide post-discharge medication management services for patients at the highest risk of misadventure.

5.7. Conclusion

One in eight elderly patients hospitalised due to an ADR had a repeat admission for ADR within 12 months of discharge. Improved medication management services at the point of discharge and in primary care are required to address preventable repeat admission due to preventable ADRs. The PADR-EC score could be routinely used at hospital discharge to screen patients who are at the highest risk of repeat ADRs to guide the use of interventions, such as medication management reviews, to prevent ADR-related hospital admissions.

CHAPTER SIX

6. Prospective Detection versus Administrative Coding of Adverse Drug Reactions leading to Hospitalisations in the Elderly

6.1. Preface

Chapter 5 discussed the findings of a study, which described the utility of an ADR score at hospital discharge in identifying elderly patients who are at higher risk of a repeat ADR-related admission. The ADR score was developed using a prospective study design, which usually has the highest detection rate as found in studies discussed in Chapter 3 and 4. It is also known that different methods of ADR detection result in the reporting of different rates of ADRs as discussed in Chapter 1. This chapter describes the findings of a study which compared the prevalence and characteristics of ADR-related admissions identified using two different methods of detection in the same study cohort.

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6.2. Abstract

Purpose: To compare prospective identification of ADR-related hospital admissions in the elderly with administrative coding of ADRs using the International Classification of Diseases 10th Revision Australian Modification (ICD-10-AM) coding system.

Methods: We linked the records of 768 enrolled patients from an earlier study, where clinical pharmacists prospectively identified ADRs, to their hospital administrative data. We identified patients in the prospective study whose admissions were coded as ADRs using ICD-10-AM codes. We then compared the prevalence and characteristics of ADRs identified by coding or prospective review by pharmacists in this patient sample.

Results: According to ICD-10-AM coding, 2.7% of patients were admitted due to ADRs, while 15.0% of patients were deemed to be admitted due to ADRs based on prospective review by clinical pharmacists. Most (85.7%) patients coded as having an ADR-related admission were also identified as such in the prospective review. Haematological (23.1%) and metabolic reactions (23.1%) were frequent causes of ADRs identified by coding, whereas cardiovascular ADRs (27.8%) were more common causes of ADRs identified prospectively by pharmacists. Antidepressants (16.7%) and cardiac glycosides (16.7%) were the most commonly implicated drug groups in ADRs identified by coding, whereas diuretics (28.8%) and renin-angiotensin system inhibitors (17.0%) were frequently implicated as causes of ADRs identified prospectively by pharmacists.

Conclusion: Reliance on administrative coding potentially underestimates the extent of the problem of ADRs as a cause of hospitalisation in the elderly, and more detailed

prospective review of admissions provides additional targets for strategies to prevent ADRs.

Key Points

- ADR detection methods in the elderly using administrative coding and prospective review result in markedly different rates and types of ADRs.
- The characteristics of ADRs identified by administrative coding and prospective review by pharmacists differ, and this has important implications when considering targets for ADR prevention strategies.

6.3. Introduction

Adverse drug reactions (ADRs) are a major public health problem in elderly accounting for 6-12% of hospital admissions [238]. Effective detection and prevention are important to tackle the global burden of ADRs, especially in the elderly. Administrative databases increasingly use the International Classification of Diseases 10th Revision (ICD-10) system to classify diagnostic, health services utilisation and death data [78]; in Australia, the Australian Modification (ICD-10-AM) is used [287]. In ICD-10-AM, adverse reactions to therapeutic agents are coded as Y40 to Y59 ('drugs, medicaments and biological substances causing adverse effects in therapeutic use excluding accidents in the technique of administration of drugs') [287]. Australian clinical coding standards allow ADR codes to be applied to any diagnosis and therefore retrospective ADR identification is possible [287].

The use of different methods of ADR detection results in studies identifying varying rates and types of ADRs, and different drug classes responsible for ADRs [51]. In one study, the frequency of ADRs causing admissions to a medical department, identified using ICD-10, was much lower (0.2% of admissions) than that identified by medical record review (5.8%) [98]. Even though there have been comparisons between the results of different study designs for ADR detection [78], there are few studies that utilise different ADR identification methods in the same cohort of patients. One such prospective observational study found that adverse drug events to outpatient medications were under-reported in emergency department administrative data compared to those detected at the point of care (3.9% versus 14.0% of presentations) [100]. Despite the burden of ADR-related admissions in the elderly, we are not aware of any studies that have utilised different ADR identification methods in the same cohort of elderly patients,

and focussed on ADRs as a cause of hospital admission. Consequently, we aimed to identify and characterise ADR-related hospital admissions in the elderly based on an administrative database utilising ICD-10-AM and compare these results with those of a prospective method of ADR detection.

6.4. Methods

We used data collected as part of a prospective cross-sectional study on ADR-related hospital admissions to medical wards in the elderly (aged ≥65 years) conducted at the Royal Hobart Hospital (RHH), Tasmania, Australia [214]. An ADR was defined as "a response to a drug that is noxious and unintended and occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [37]. ADR-related admissions were prospectively identified from detailed review of medical records and patient interviews followed by consensus agreement between two expert clinical pharmacists. The methodology has been published elsewhere [214]. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (Appendix 1).

For this analysis, we linked the records of the 768 patients reviewed prospectively (March 2014 to March 2015) to their hospital administrative data using their medical record number (patient identifier) and identified clinical coding instances of ADR-related diagnoses (ICD-10-AM codes Y40 to Y59). The patients' medical records were reviewed, and we excluded ADRs that occurred while patients were in hospital. All patients coded as having an ADR-related admission were initially categorised by the primary clinical pharmacist researcher. These cases were assessed independently and blindly by a senior clinical pharmacist. A consensus decision was

reached if there was a discrepancy between the two clinical pharmacists' assessments. The consensus decision was based on a further discussion and comprehensive review of the coded ADR cases. For each method of identification, we determined the proportion of ADR-related admissions, commonly implicated drugs and clinical manifestations of ADRs. The causality and preventability of ADRs were evaluated using the Naranjo algorithm (Appendix 8) [179] and modified Schumock Thornton criteria [221], respectively. ADRs were classified as definite (score from 9 to 12), probable (score from 5 to 8), possible (score from 1 to 4), or doubtful (score from 0 to -2), with only definite and probable ADRs being considered for this study

Data were analysed descriptively using SPSS version 20.0 (SPSS Inc, Chicago, Illinois) and presented as number and percentages.

6.5. Results

ADR-related ICD-10-AM codes were assigned to 51 of the 768 patients. Of these, 29 cases were excluded since the ADR diagnoses were coded based on ADRs occurring during hospitalisation, and one patient was excluded due to an incorrect Y code, leaving 21 (2.7%) patients to be included in the analysis. Of the 21 patients with ADRs, 17 (81%) had a single ADR, three (14.3%) had two ADRs, and one (4.8%) had three ADRs. In 19 (90.5%) cases, the ADRs were caused by a single drug, and in two (9.5%) cases, the ADRs were caused by a combination of drugs. Thus, there were a total of 26 ADRs caused by 24 drugs contributing to all ADR-related admissions identified by administrative coding.

In contrast, 115 patients (15.0%) were judged by clinical pharmacists following prospective review as being admitted due to ADRs. In these patients, a total of 194 ADRs

caused by 264 drugs were identified. Most of the ADR-related admissions identified by coding (n=18, 85.7%) and prospective review (n=106, 92.2%) were considered 'preventable'. Using the Naranjo algorithm, 81.0% (n=17) of admissions that were coded as ADRs were deemed 'probable' and 19.0% (n=4) 'definite', whereas there were 106 (69.3%) probable and nine (5.8%) definite ADRs identified based on prospective review. A comparison of the characteristics of ADR-related admissions identified by administrative coding and prospective review by clinical pharmacists is presented in Table 17.

Table 17. Characteristics of adverse drug reaction-related admissions identified using the administrative coding and prospective review

Characteristic	ADRs identified from administrative coding	ADRs identified from prospective review
Total number of ADRs identified	**n=26**	**n=194**
Types of ADR (n, %)		
Haematological	6 (23.1)	20 (10.3)
Endocrine and metabolic	6 (23.1)	26 (13.4)
Neuropsychiatric	5 (19.2)	34 (17.5)
Gastrointestinal	4 (15.4)	17 (8.8)
Cardiovascular	3 (11.5)	54 (27.8)
Renal and genitourinary	-	34 (17.5)
Neuromuscular and skeletal	1 (3.8)	6 (3.1)
Dermatological/allergic	-	1 (0.5)
Others	1 (3.8)	2 (1.0)
Total number of drugs causing ADRs	**n=24**	**n=264**
Drug classes implicated (n, %)		
Antidepressants	4 (16.7)	14 (5.3)
Cardiac glycosides	4 (16.7)	5 (1.9)

Characteristic	ADRs identified from administrative coding	ADRs identified from prospective review
Diuretics	3 (12.5)	76 (28.8)
Anti-Parkinson drugs	3 (12.5)	5 (1.9)
Opioids	2 (8.3)	7 (2.7)
Immunosuppressants	2 (8.3)	6 (2.3)
Antithrombotic agents	2 (8.3)	17 (6.4)
Antineoplastic agents	1 (4.2)	2 (0.8)
Benzodiazepines	-	10 (3.8)
β-Blocking agents	1 (4.2)	17 (6.4)
NSAIDs	-	3 (1.1)
Antiepileptics	1 (4.2)	5 (1.9)
RAS inhibitors	-	45 (17.0)
Calcium channel blockers	-	15 (5.7)
Vasodilators used in cardiac diseases	-	6 (2.3)
Others	1 (4.2)	31 (11.7)

Abbreviations: ADR, adverse drug reaction; NSAIDs, nonsteroidal anti-inflammatory drugs; RAS, renin-angiotensin system.

The prevalence of ADRs identified by administrative coding (2.3%) was much lower than that identified by prospective review (15.0%). Haematological (23.1%) and metabolic reactions (electrolyte disturbances) (23.1%) were frequently identified using the administrative coding, whereas cardiovascular ADRs (27.8%) were commonly identified by prospective review. Antidepressants (16.7%) and cardiac glycosides (16.7%) were the most commonly implicated drug groups in ADRs identified by administrative coding, whereas diuretics (28.8%) and renin-angiotensin system (RAS) inhibitors (17%) were frequently implicated in ADRs identified by prospective review.

Most (18, 85.7 %) of the 21 patients coded as having ADR-related admissions were also identified in the prospective review. Among these, 17 (81.0 %) patients were coded with the same ADRs caused by the same drug classes as in the prospective study. However, one (4.8%) patient was coded with a different ADR, and in three (14.3%) patients, the coded ADRs were not identified in the prospective study. Thus, the admission of a total of 118 patients was identified by either administrative coding or prospective review as being due to an ADR. The overlap in the identification of ADR-related admissions identified by administrative coding and prospective review is outlined in Figure 4.

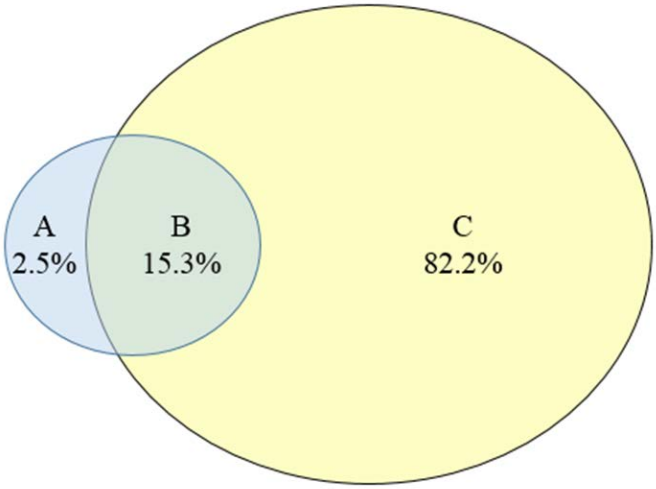

Figure 4. Comparison of hospital admissions due to adverse drug reactions (n=118) identified by administrative coding alone (A), administrative coding and prospective review (B) and prospective review alone (C)

6.6. Discussion

Almost 3% of elderly patients admitted to medical wards of an Australian hospital were coded as having an ADR-related admission. Other international studies using

administrative coding have reported similar ADR rates (2.7–3.9%) although these studies were not focussed on the elderly [85, 100]. Our estimate based on administrative coding was much lower than the figure of 15.0% identified by prospective review. The discrepancy between the two methods of ADR identification is an expected finding. This discrepancy could be due to clinical pharmacists being more skilled in the identification of ADRs and more comfortable with their reporting than their medical colleagues. There is strong evidence that pharmacists report a higher rate of adverse drug events compared to non-pharmacists [226]. A systematic review of prospective observational studies reported a similarly high rate (10.7%) of ADR-related admissions in the elderly [53]. Additionally, medical staff (usually junior doctors) may be hesitant to assign an ADR-related diagnosis in the absence of clear evidence of drug-induced disease [288], and hence fewer ADRs may have been identified using the administrative data.

Differences were seen in the type of ADRs and drug classes responsible for the identified ADRs. ADRs detected by administrative coding were more likely to involve additional treatment, or abnormal laboratory tests and/or elevated drug levels, rather than drug cessation or dose adjustment. Also, patients whose admissions were related to a more obvious consequence of an ADR, such as a fall or functional impairment, might have been prioritised for documentation as an ADR in the administrative database. On the other hand, prospective review allowed us to comprehensively assess the different drug classes, including concomitant drugs possibly contributing to an ADR, and detect more ADRs. Prospective review identified more cardiovascular ADRs, largely hypotension/orthostatic hypotension/syncope, than the database study; perhaps because doctors might be more likely to attribute ADR signs to an underlying disease, and pharmacists to a drug.

Both ADR-reporting methods have limitations. In studies that rely on the coding of ADRs, ADRs may be under-reported due to under-recognition and under-recording of ADR diagnoses by medical staff and limitations of the coding system [289]. Even though prospective review was expected to comprehensively identify ADRs, there is inevitably some subjectivity in this process as seen in the present study, in which the administrative coding identified three ADR cases that were not identified using the prospective review. Another inherent limitation to the use of administrative databases is wrong or incomplete information [85]; while labour and cost may be prohibitive to prospective ADR identification [100].

In conclusion, our study suggests that reliance on coded ADRs identifies only a small proportion of ADR-related events and perhaps only certain types of events contributing to hospital admission. ADR identification using coding alone may under-estimate the ADR incidence or bias the findings in relation to drugs causing ADR-related admissions. Administrative coding is entrenched and easy to access, while prospective review is intensive and time-consuming, but yields more information which can be used to identify additional targets for interventions to prevent ADR-related admissions.

CHAPTER SEVEN

7. General Discussion and Conclusion

7.1. Preface

The overall aim of this thesis was to develop and validate a method of identifying elderly patients who are at risk of an adverse drug reaction (ADR)-related hospital admission. To achieve this aim, a narrative literature review and a prospective study including four subset analyses were undertaken. The rationale, objectives, methods, findings, and limitations of each study analysis have been presented in detail in previous chapters (Chapter 3, 4, 5 and 6). The final section of this thesis will summarise the overall findings of the thesis and discuss the practical implications and future research directions.

7.2. General discussion

ADRs represent a major burden on health care [3, 86], which necessitate a major shift in the nature and delivery of ADR prevention strategies that would reduce the burden of ADRs, particularly in older patients. This work has developed and validated a simple and practical tool, the 'PADR-EC' (Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients) score to identify community-dwelling elderly patients at risk of hospitalisation due to preventable ADRs. To the best of our knowledge, this is the first tool developed for such a purpose in the field of ADRs. The tool was developed from two prospective studies conducted in two different Tasmanian hospitals, which utilised an intensive ADR detection method. These studies further enhanced the understanding of ADR-related hospital admissions and the potential

risk factors among the older population. Our data showed that almost one in five unplanned medical ward admissions in elderly Australians were ADR-related, and one in eight patients had a repeat ADR-related admission within 12 months of discharge. Clearly, the problem of ADRs leading to admissions or repeated admissions is persisting in elderly Australians despite the available strategies for ADR prevention, so additional strategies are needed. It could also be that the available strategies for ADR prevention are being implemented in a sub-optimal manner. Against this backdrop, the newly developed PADR-EC score is highly relevant to prevent ADR-related hospital admissions. The sensitivity of the score was found to be 72% which indicates that the score is a good predictor of ADR-related admissions though the specificity was found to be low (Chapter 4). The score could be used at the time of hospital discharge to identify patients requiring intensive intervention to prevent ADR-related repeat admissions since our repeat admission study (Chapter 5) found that the PADR-EC score among those who were readmitted due to ADRs within 12 months of hospital discharge was higher than those who were not. Hence, the development and validation of the PADR-EC score is a crucial step towards the reduction of ADRs in the older population.

Our prospective analysis of ADRs as a cause of admission to hospital in the elderly found that almost 90% of ADR-related admissions were preventable. These findings suggest that the available systems of preventing medication misadventure are not adequate for elderly Australians, corroborating the findings of previous community-based studies [5, 88, 290]. Cardiovascular drugs, especially antihypertensives, were commonly implicated in ADR-related admissions and repeat admissions in the elderly, due to hypotension, orthostatic hypotension, syncope, dizziness and acute kidney injury. A combination of two or more drugs sharing a similar ADR profile was involved in the

majority of ADR cases (e.g., hypotension) in our study which warrants urgent attention by prescribers. Additionally, three among the four deaths that were observed in our study due to the severe ADRs were due to cardiovascular medications. Cardiovascular agents (anticoagulants) were found to be one of the most common drug classes associated with ADR-related mortality in a study reported in United States [68]. In another large prospective study, amongst the overall fatality (0.15%) of ADR-related admissions, cardiovascular medications (antihypertensives and anticoagulants) were responsible for most of the deaths. [58]. The 2016 National Heart Foundation guidelines in Australia suggest a patient-centred approach in the management of hypertension, balancing the benefits of blood pressure lowering medications versus patients' experiences of adverse drug effects [291]. The guidelines suggest starting with low-to-moderate doses of antihypertensive medications and gradually increasing to minimise ADRs such as hypotension. Additionally, listening carefully to patients and verifying temporal relationships between drug treatment changes and clinical effects can strengthen recognition of ADRs and improve management through timely intervention [286, 291]. This is particularly important when patients are taking a combination of antihypertensive medications.

When administering multiple medications, the ADRs associated with either drug could be enhanced [292] or sometimes, the adverse effects of some drug combinations may also be synergistic [66]. In this scenario, drug-drug interactions (DDIs) also play a potential role in inducing ADRs [173], such as severe hypotension. In our study, almost 43% of ADR-related admissions involved potentially relevant DDIs. The DDIs between antihypertensive medications have been well established. For example, the prescribing information for angiotensin converting enzyme inhibitors (ACEIs) or diuretics states that

co-administration may result in excessive blood pressure reduction [293, 294]. The recommendations include temporarily stopping or reducing diuretic dosing for three days before starting or increasing the dose of an ACEI. Orthostatic hypotension and antihypertensive drugs are associated with falls among older people [295, 296]. Minimisation of medications including the withdrawal (deprescribing) of causative medications is one of the intervention strategies to prevent falls in the elderly [297]. Deprescribing in the elderly has demonstrated a significant reduction in mortality [235]. Overall, we suggest that increased ADR-related hospital admissions from cardiovascular medications, especially antihypertensive drugs, warrant urgent attention to additional strategies of prevention.

Elderly patients with a history of an ADR-related hospitalisation were more vulnerable to repeat ADR-related hospital admission. In our study, more than half of the repeat ADRs were caused by the same medications as at the index admission. Our data suggest that interventions are needed to reduce repeat ADR-related hospital admissions in elderly patients. High-risk medications (e.g., diuretics) that contribute to a patients' admission must be reviewed carefully at hospital discharge with frequent post-discharge monitoring. In a randomised open-label trial, although underpowered, discharge-planning intervention combining chronic medication review, education, and enhanced transition-of-care communication was associated with 39.7% fewer readmissions related to ADRs [286]. Pharmacist medication review, patient counselling, and telephone follow-up were associated with a lower rate of preventable adverse drug events 30 days after hospital discharge in another randomised trial [138].

The transition from hospital to home is a potentially vulnerable period for ADRs [298]. Promoting effective transitions of care at hospital discharge including

improvements in communication between inpatient and primary care physicians, effective medication reconciliation at discharge, adequate patient education about their medication use and recent drug changes, closer medical follow-up, engagement with social support systems, and greater clarity in physician–patient communication [299] might help to prevent ADRs in the post-discharge period. There is also need for more comprehensive medication review and reconciliation at hospital discharge and ongoing monitoring in primary care to prevent ADR-related admissions in the elderly. The present system of annual home visits (Home Medicines Review) by pharmacists may not be adequate in reducing ADRs in these complex elderly patients. The greater number of ADR-related hospital admissions found in our study suggests that these patients require more intensive and frequent monitoring to prevent ADR recurrence. We suggest there is a need to change existing medication management service models. Identifying elderly patients at risk of ADR-related admissions is the initial step followed by necessary intervention (e.g., alteration or substitution of high-risk medications) and frequent monitoring of these patients. This role could be handled by a team of general practitioner (GP), pharmacist, consultant pharmacist or practice nurse. We suggest coordination of these activities by pharmacists who can work collaboratively with GPs in primary care settings. We also suggest having pharmacists in general practices with access to all the available data to drive the medication safety agenda in primary care to prevent ADR-related admissions in the community-dwelling older population.

Despite the concerns about ADRs, there is insufficient information regarding the risk factors for ADR-related hospital admissions in community-dwelling patients, mainly due to the limited number of studies that have been performed in community settings [52, 238]. Additionally, there are a lack of prospective Australian studies in community

settings that have focused on this issue. A previous prospective ADR study in elderly Australians mainly investigated the frequency, severity, and preventability of ADR-related admissions rather than identifying the potential risk factors for admissions [88]. Most of the other prospective studies were conducted among the general population [300, 301]. A few retrospective studies were conducted in Australian community settings using administrative databases (e.g., administrative claims data from the Australian Department of Veterans' Affairs) [302-306], but findings from these studies were limited due to the high chance of missing potential adverse reactions using the retrospective approach. This was highlighted in our coding study (Chapter 6), in which the frequency of ADRs causing admissions to a medical ward identified using an administrative database was much lower than that identified by the prospective review (Chapter 4). Prospective studies with intensive monitoring of ADRs provide us with a greater range of events, and potentially a better understanding of the risk factors involved. We, therefore, believe that our work addressed a significant gap in the literature. Our study identified various risk factors predicting ADR-related admissions in the elderly. The number of antihypertensive medications was found to be the strongest predictor of an ADR, followed by using inappropriate anticholinergics, renal failure, dementia and drug changes within the preceding three months. These risk factors were assigned a score, and the ADR risk score was computed based on the sum of scores of individual risk factors. We identified that patients with a PADR-EC score of ≥6 have a high chance of ADR-related admission. The predictive ability of the PADR-EC score was found to be 0.70 [95% confidence interval (CI) 0.65–0.75] suggesting the ability of the PADR-EC score to predict ADR-related admissions is high. The score was validated with a predictive ability of 0.67 (95% CI

0.56–0.78) in another hospital (the Launceston General Hospital) suggesting that the findings are generalisable.

7.3. Practice implications

The PADR-EC score has a wide range of potential applications in clinical and pharmaceutical care services in different healthcare settings. The score could be used in primary care settings and at the point of hospital discharge so that primary care-based medication management services could be targeted to the patients at highest risk. It could be implemented as a routine tool during the process of medication review, particularly at the point of discharge of elderly patients. Available studies on medication reviews had different foci, and the findings from a recent systematic review showed that only one-quarter of studies evaluated the impact of medication review on ADR-related outcomes [127]. Currently, there is a lack of clear evidence on the effectiveness of medication reviews on outcomes related to ADRs. This might be due to an improper targeting of medication reviews, possibly based on the current guidelines that identify high-risk patients. Furthermore, there are often other factors such as patient complexity and the variety of recommendations made to address a range of heterogeneous outcomes (e.g., the number of drugs or potentially inappropriate medicines, drug overuse, the number of GP visits, medication adherence, medication management, etc.). It might be that medication reviews are effective, but we are perhaps not investigating the right outcomes to measure the impact of medication review services. We suggest that, if we want to measure the effectiveness of medication reviews on important outcomes like ADR-related hospitalisation, we need to target these service at the risk factors identified in our study. In addition, the medication review studies might have looked at ADRs detected retrospectively (e.g., coded ADRs) which identify fewer events. We suggest that there is

a need for changing the eligibility criteria for medication reviews; medication reviews might be better targeted using the PADR-EC risk score, in addition to other criteria deemed to be important in preventing ADR-related hospital admissions based on the local context and clinical judgement. During a clinical medication review, the risk factors identified in our study could be easily retrieved from the patients' clinical notes or through a direct patient interview.

The PADR-EC tool could also be applied during the medication reconciliation process especially in transitions of care. Previous studies of medication reconciliation programs at hospital transitions identified outcomes mostly related to medication discrepancies, but not the risk of ADRs [131]. In transitions of care, there are high chances of medication discrepancies and DRPs [307]. Hence identifying and targeting high-risk patients for ADRs using the score in this setting is also feasible. In adult patients, medication reconciliation reduced adverse drug event-related hospital revisits (relative risk reduction of 67%) [136]. Applying the PADR-EC score during the medication reconciliation process would enhance the reduction of ADR-related hospital revisits by identifying high-risk patients for follow-up interventions. ADR risk stratification during medication review or medication reconciliation and communication of this risk, together with recommendations that target the specific risk factors identified, to prescribing physicians or GPs at discharge are likely to reduce the risk of ADR-related hospitalisation. Integrating the score into prescribing software, such as computerised physician order entry and clinical decision support systems, could alert the prescribing physicians to patients' risk of ADRs and subsequent admissions. Thus, we believe that the PADR-EC score is a practical tool that could be readily incorporated into clinical processes to assist clinical teams in hospitals and allow GPs to provide better-informed

post-discharge medication management to their patients in collaboration with other primary healthcare providers.

7.4. Future directions

While this thesis has demonstrated the potential of an ADR prediction score, there are opportunities for extending the scope of this work. Future research should endeavour to do the following;

- Validate the applicability of the PADR-EC score in different populations from various settings.
- Investigate the effectiveness of PADR-EC score guided medication review on ADR-related hospitalisation in appropriately designed prospective studies with tailored interventions to address the risk factors of ADR-related admissions in the elderly.
- Conduct further prospective studies on ADR-related admissions in other regions of Australia to further enhance the understanding of ADR burden in the elderly.
- Conduct future studies focussing on the contributive role of immunological or idiosyncratic reactions ADRs causing hospital admissions in the complex older population.
- Conduct further larger studies on repeat admissions due to ADRs in the older population and investigate the utility of the PADR-EC score.

7.5. Conclusion

Collectively, the work in this thesis has addressed several important gaps in knowledge in relation to ADRs leading to hospital admissions in the older population. Overall, the thesis highlighted the importance of a tool for prevention of ADR-related hospital

admission in the elderly, and successfully developed and validated such a tool to identify patients at risk of these ADRs. The tool can readily target elderly patients that can benefit from interventions aimed to alleviate ADR-related consequences such as hospital admissions. This work also has highlighted that a more detailed prospective review of admissions gave a clearer understanding of the number of ADRs for directing appropriate medication management services towards addressing the problem. Overall, this thesis has significantly added to the literature on hospitalisation due to ADRs, and the findings have the potential to make a major contribution to clinical practice and policy.

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APPENDICES

Appendix 1. Institutional ethics approvals

1. A. Prospective study at Royal Hobart Hospital

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HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

05 February 2014

AssocProf Luke Bereznicki
School of Medicine
University of Tasmania

Sent via email

Dear AssocProf Bereznicki

REF NO: H0013773
TITLE: Predicting Adverse Drug Reactions (ADRs) in Elderly Patients admitted to the Royal Hobart Hospital (RHH)

Document	*Version*	*Date*
Application Form – Low Risk	-	20 Jan 2014
Participant Questionnaire	June 2013	20 Jan 2014
Privacy Form	-	20 Jan 2014
Participant Information Sheet and Consent Form	June 2013	20 Jan 2014
Flow Chart	June 2013	20 Jan, 2014

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **31 January 2014** to be conducted at the following site(s):

Royal Hobart Hospital

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2009).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested.
http://www.research.utas.edu.au/human_ethics/medical_forms.htm

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 31/05/2015. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 6254.

Yours sincerely

Janette Smith
Ethics Administrator

1. B. Prospective study at Launceston General Hospital

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

31 August 2015

Assoc Prof Luke Bereznicki
School of Medicine
University of Tasmania

Sent via email

Dear Assoc Prof Bereznicki

REF NO: H0015152
TITLE: Predicting Hospitalisation due to Adverse Drug Reactions (ADRs) in Older Patients

Document	*Version*	*Date*
Tasmanian HREC Low Risk Application Form	-	August 2015
Tasmanian HREC Privacy Form	-	August 2015
Particpant Consent Form	Version 1	14 July 2015
Interview questions for study participants	Version 1	14 July 2015
Participant information Sheet	Version 1	14 July 2015

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **31 August 2015** to be conducted at the following site(s):

Launceston General Hospital

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested.

http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due **31 August 2016.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 6254.

Yours sincerely

Digitally signed by Lynda Hobman
DN: cn=Lynda Hobman, o, ou, email=lynda.hobman@utas.edu.au, c=AU
Date: 2015.08.31 09:41:18 +10'00'

Lynda Hobman
Administration Officer (Integrity and Ethics)
Research Integrity and Ethics Unit
Office of Research Services
University of Tasmania

1. C. Retrospective study (repeat ADR-related admissions study) at Royal Hobart Hospital

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

19 April 2016

AssocProf Luke Bereznicki
C/o- Pharmacy

Sent via email

Dear AssocProf Bereznicki

REF NO: H0015610
TITLE: Re-admission due to Adverse Drug Reactions in Elderly community-dwelling Patients

Document
Application Form – Low Risk
Privacy Form
Figure 1(Re-Admission due to ADRs)

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **01 April 2016** to be conducted at the following site(s):

Royal Hobart Hospital

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due **01 April 2017.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Heather Vail
Ethics Administrator
Office of Research Services
Email: Heather.vail@utas.edu.au
University of Tasmania
Private Bag 01 Hobart Tas 7001

Appendix 2. Patient consent form and participant information sheets

2. A. Patient consent form (Prospective studies at Royal Hobart and Launceston General Hospitals)

Private Bay 26 Hobart
Tasmania, Australia 7001
Phone (03) 6226 2190 Fax (03) 6226 2870
Email: pharmacy@utas.edu.au

PHARMACY, SCHOOL OF MEDICINE

CONSENT FORM

Title of Project: "Prediction of Adverse Drug Reactions (ADRs) Causing Older People to be admitted to Hospital"

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1. I acknowledge that the nature, purpose and contemplated effects of the project so far as it affects me, have been fully explained to my satisfaction by the research worker and my consent is given voluntarily.

2. The details of the project methods have also been explained to me, including the anticipated length of time it will take and an indication of any discomfort, which may be expected. I understand that my involvement means that the research officer has my permission to collect information from my medical records, and that I will be asked to participate in an interview with the research officer.

3. I understand that these are the following risks or possible discomfort:

- Possible discomfort due to the underlying medical condition.
- Possible discomfort due to not understanding clearly the scientific reasons for the questions being asked.
- Discomfort trying to remember the events before admission or medication history asked about by the research officer.

I am aware that if I become distressed during the interview, I may either end the interview or ask the researcher to move the discussion in another direction. If necessary, counselling will be arranged for me or at no expense to me.

4. Although I understand that the purpose of this research project is to improve the quality of medical care, it has also been explained that my involvement may not be of any benefit to me.

5. I have been given the opportunity to have a member of my family or friend present while the project was explained to me.

6. I am informed that no information regarding any medical history will be divulged and the results of any analyses involving me will not be published so as to reveal my identity.

7. I understand that my involvement in the project will not affect my relationship with my medical advisers in their management of my health. I also understand that I am free to withdraw from the project at any stage and any of my data that have been collected. My withdrawal will not affect my legal rights, my medical care or my relationship with the hospital or my doctors.

8. I understand that I will be given a signed copy of this patient information sheet and consent form. I am not giving up my legal rights by signing this consent form.

9. I understand that the study will be conducted in accordance with the latest versions of the National Statement on Ethical Conduct in Human Research 2007 and applicable privacy laws.

Name of participant"_____

Signature of participant _____ Date_____

10. I have explained this project and the implications of participation in it to this volunteer and I believe that the consent is informed and that he/she understands the implications of participation.

Name of investigator: _____

Signature of investigator:_____ Date: _____

2. B. Participant information sheet (Prospective study at Royal Hobart Hospital)

Private Bay 26 Hobart
Tasmania Australia 7001
Phone (03) 6226 2190 Fax (03) 6226 2870
Email: pharmacy@utas.edu.au

PHARMACY, SCHOOL OF MEDICINE

"Prediction of Adverse Drug Reactions (ADRs) Causing Older People to be Admitted to Hospital" --Participant Information Sheet

You are invited to participate in a research study, conducted by the University of Tasmania, School of Medicine. You were selected as a possible participant in this research because you are 65 years of age or older, and were admitted to a medical ward of the Royal Hobart Hospital (RHH) between March 2014 and March 2015.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is the background of this study?

Complications related to medicines are an increasingly important health concern. Older patients have a higher chance for developing more than one disease. Also, as we age, there are changes in the body systems which may imitate a disease condition. Because of these reasons, older people are more likely to be prescribed medication by their doctors and to take multiple medicines. This puts them at a higher risk of suffering adverse drug reactions (ADRs). Between 1 in 20 and 1 in 3 older people living in the community will experience an ADR.

2. What is an adverse drug reaction (ADR)?

Adverse reactions to drugs are common. Most are predictable and are known as side effects. Common examples include diarrhoea caused by antibiotics and drowsiness caused by some anti-allergy medicines.

3. What is the purpose of this study?

This study aims to investigate ADRs that cause older people to be admitted to hospital, including what causes them, how severe they are and whether they can possibly be prevented. The overall aim is to develop a 'score' for predicting which older people are likely to need to be admitted to hospital because of an ADR. The hope is that this score will be used to help identify people living in the community who have a high chance of ADRs, so that they can receive additional care and attention from healthcare professionals to reduce their chance of ending up in hospital.

This project will form a part of Nibu Parameswaran Nair's PhD thesis.

4. What does this study involve?

If you agree to participate in this study, you can indicate that you want to be involved in using the attached Participant Consent Form. The study will be conducted over 12 months from March 2014 to March 2015.

This study consists of two methods. Firstly, you will be interviewed with a short questionnaire regarding any recent changes to your drug therapy, how you take your medicines, alcohol use, smoking status, and previous ADRs. The interview will last not more than 30 minutes. Secondly, your medical records at the RHH will be reviewed to determine whether you experienced an ADR and what factors contributed to any ADR that may have occurred.

5. What are the risks associated with these procedures?

You are unlikely to experience any discomfort during this procedure. If you experience some discomfort during the interview process, it may be due to the following reasons

a) Possible discomfort due to the underlying medical condition.

b) Possible discomfort due to not understanding clearly the scientific reasons for the questions being asked.

c) Discomfort trying to remember the events before admission or medication history asked about by the research officer.

If you find that you are becoming distressed during the interview, you are free to either end the interview or ask the researcher to move the discussion in another direction. If necessary, we will arrange for you to see a counsellor at no expense to you.

6. What are the benefits of this study?

Your participation may contribute to a better understanding of ADRs occurring in older people. This may lead to future improvements in ADR prediction for people like you, with the aim of reducing the risks of ADRs for these people. This study also assists health practitioners to identify people who are at increased risk of ADRs and promote safer use of medicines, with a subsequent reduction in the associated costs of admissions due to ADRs.

7. What happens if I don't want to take part in the study?

Participation is entirely voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect your future care.

8. How will my confidentiality be protected?

Of the people treating you, only the research pharmacist will know whether or not you are participating in this study. All information will be treated in a confidential manner and all data, including your personal information, will be coded against a unique identifying number so your personal information will be protected. Your name and any other personal information will not be used in reports or publications resulting from this study. All of the information collected as part of this research will be kept in secure storage in the School of Medicine and will be destroyed after a period of 10 years in line with University regulations.

9. Will I benefit from the study?

This study aims to further medical knowledge and may prevent older people experiencing ADRs in the future; however it will may directly benefit you.

10. What should I do if I want to discuss this study further before I decide?

When you have read this information, if you have any queries regarding this study or your participation in this study, please do not hesitate to contact one of the study investigators listed below:

Nibu Parameswaran Nair (PhD candidate)
Telephone: 0469417704; Email: nnair@utas.edu.au
Associate Professor Luke Bereznicki (Deputy Head, School of Medicine)
Telephone: 0438232864; Email: Luke.Bereznicki@utas.edu.au
Dr Leanne Chalmers (Lecturer, Pharmacy, School of Medicine)
Telephone: 0417919369; Email: Leanne.Chalmers@utas.edu.au
Dr Ronald Castelino (Lecturer, Pharmacy, School of Medicine)
Telephone: 0406360715; Email: Ronald.Castelino@utas.edu.au
Professor Gregory Peterson (Professor, Pharmacy, School of Medicine)
Telephone: 62261080; Email: G.Peterson@utas.edu.au
Michael Connolly (Senior Clinical Pharmacist)
Telephone: 03 6222 8485; Email: Michael.Connolly@dhhs.tas.gov.au

11. Who should I contact if I have concerns about the conduct of this study?

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 7479 or human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote the ethics reference number **H0013773**

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.

2. C. Participant information sheet (Prospective study at Launceston General Hospital)

Private Bay 26 Hobart
Tasmania Australia 7001
Phone (03) 6226 2190 Fax (03) 6226 2870
Email: pharmacy@utas.edu.au

PHARMACY, SCHOOL OF MEDICINE

"Prediction of Adverse Drug Reactions (ADRs) Causing Older People to be Admitted to Hospital" ---- Participant Information Sheet

You are invited to participate in a research study, conducted by the University of Tasmania's School of Medicine. You were selected as a possible participant in this research because you are 65 years of age or older, and were admitted to a medical ward of the Launceston General Hospital (LGH) between August 2015 and February2016.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. What is the background of this study?

Complications related to medicines are an increasingly important health concern. Older patients have a higher chance for developing more than one disease. Also, as we age, there are changes in the body systems that may imitate a disease condition. Because of these reasons, older people are more likely to be prescribed medication by their doctors and to take multiple medicines. This puts them at an increased risk of suffering adverse drug reactions (ADRs). Between 1 in 20 and 1 in 3 older people living in the community will experience an ADR.

2. What is an adverse drug reaction (ADR)?

Adverse reactions to drugs are common. Most are predictable and are known as side effects. Common examples include diarrhoea caused by antibiotics and drowsiness caused by some anti-allergy medicines.

3. What is the purpose of this study?

This study aims to investigate ADRs that cause older people to be admitted to hospital, including what causes them, how severe they are and whether they can possibly be prevented. The overall aim is to develop a 'score' for predicting which older people are likely to need to be admitted to hospital because of an ADR. The hope is that this score will be used to help identify people living in the community who have a high chance of ADRs, so that they can receive additional care and attention from healthcare professionals to reduce their chance of ending up in hospital.

This project will form a part of Nibu Parameswaran Nair's PhD thesis.

4. What does this study involve?

If you agree to participate in this study, you can indicate that you want to be involved in using the attached Participant Consent Form. The study will be conducted over 6 months from August 15th 2015 to February 15th 2006. This study consists of two methods. Firstly, you will be interviewed with a short questionnaire regarding any recent changes to your drug therapy, how you take your medicines, alcohol use, smoking status, and previous ADRs. The interview will last not more than 20 minutes. Secondly, your medical records at the LGH will be reviewed to determine whether you experienced an ADR and what factors contributed to any ADR that may have occurred.

5. What are the risks associated with these procedures?

You are unlikely to experience any discomfort during this procedure. If you experience some discomfort during the interview process, it may be due to the following reasons

a) Possible discomfort due to the underlying medical condition.

b) Possible discomfort due to not understanding clearly the scientific reasons for the questions being asked.

c) Discomfort trying to remember the events before admission or medication history asked about by the research officer.

If you find that you are becoming distressed during the interview, you are free to either end the interview or ask the researcher to move the discussion in another direction. If necessary, we will arrange for you to see a counsellor at no expense to you.

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7. What happens if I don't want to take part in the study?

Participation is entirely voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect your future care.

8. How will my confidentiality be protected?

Of the people treating you, only the research pharmacist will know whether or not you are participating in this study. Your name will be removed from any data collected, and replaced with an identification number. Also, your name and any other personal information will not be used in reports or publications resulting from this study. All of the information collected as part of this research will be kept in secure storage in the School of Medicine and will be destroyed after a period of 10 years in line with University regulations.

9. Will I benefit from the study?

This study aims to further medical knowledge and may prevent older people experiencing ADRs in the future; however it may not directly benefit you.

10. What should I do if I want to discuss this study further before I decide?

When you have read this information, if you have any queries regarding this study or your participation in this study, please do not hesitate to contact one of the study investigators listed below:

Nibu Parameswaran Nair (PhD candidate)
Telephone: 0469417704; Email: nnair@utas.edu.au
Associate Professor Luke Bereznicki (Deputy Head, School of Medicine)
Telephone: 0438232864; Email: Luke.Bereznicki@utas.edu.au
Dr Leanne Chalmers (Lecturer, Pharmacy, School of Medicine)
Telephone: 0417919369; Email: Leanne.Chalmers@utas.edu.au
Dr Bonnie Bereznicki (Lecturer, Pharmacy, School of Medicine)
Telephone: 6226 2191; Email: Bonnie. Bereznicki@utas.edu.au
Dr Ronald Castelino (Lecturer, Pharmacy, School of Medicine)
Telephone: 0406360715; Email: Ronald.Castelino@utas.edu.au
Professor Gregory Peterson (Professor, Pharmacy, School of Medicine)
Telephone: 62261080; Email: G.Peterson@utas.edu.au
Michael Connolly (Senior Clinical Pharmacist)
Telephone: 03 6222 8485; Email: Michael.Connolly@dhhs.tas.gov.au

11. Who should I contact if I have concerns about the conduct of this study?

This project has been approved by the Tasmanian Health and Medical Human Research Ethics Committee. If you have any concerns of an ethical nature, or complaints about the manner in which the study is conducted, you may contact the Executive Officer of the Human Research Ethics Committee (Tasmania) Network on (03) 6226 6254 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote the ethics reference number H0015152

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.

Appendix 3. Data collection form

Predicting Adverse Drug Reaction-related Hospitalisation in Elderly Patients			
Date of admission:	Date of discharge:	Post Code:	Weight (kg):
Height (cm):	**Sex:** □ Male □ Female	Date of Birth:	Number of admissions in preceding month:
Living Status: □ Alone □ With family/friends □ Nursing home			Number of admissions in preceding three months

Comorbid conditions:

□ AIDS	□ Any tumour
□ Cerebrovascular disease	□ Hemiplegia or paraplegia
□ Chronic respiratory disease	□ Leukaemia
□ Congestive heart failure	□ Lymphoma
□ Connective tissue disease	□ Myocardial infarction
□ Dementia	□ Diabetes mellitus with end organ damage
□ Peripheral vascular disease	□ Diabetes mellitus without end organ damage
□ Peptic ulcer disease	□ Mild liver disease
□ Moderate or severe liver disease	□ Moderate or severe renal disease
□ Metastatic solid tumour	□ Others (Specify

Previous ADR: □ Yes □ No	**Admission diagnosis:**	**Charlson Comorbidity Index:**	**Barthel (ADL) Score:**

Patient outcome: □ Discharged home □ Transferred to another hospital or nursing home □ Death

Se Cr:	eGFR:	Serum drug level if any:	Albumin:	AST:
ALT:	GGT:	ALP:	Bilirubin:	Hb:
INR:	**Possible ADR-related admission:** □ Yes □ No	**Cognitive impairment:** □ Yes □ No	Fibrinogen:	PT (secs):

Medications taken prior to hospital admission

Drug Name(s) including OTC and herbal medicines	Brand name if any	Dose	Frequency	Route	Notes

ADR Nature /Description:

ADR outcome:

□ Fatal □ Not yet recovered □ Recovered □ Unknown

Drug outcome:

□ Drug stopped □ Drug withheld □ Drug continued □ Drug substituted □ Dose reduced

ADR classification:

□ Toxicity □ Side effect □ Drug Interaction □ Immunological

Causality	Preventability	Severity	Implicated Medications
□ Definite (≥9)	□ Preventable	□ Severe	1.
□ Probable (5-8)	□ Not preventable	□ Moderate	2.
□ Possible (1-4)			3.
□ Doubtful (≤0)			4.

Appendix 4. Questionnaire to study participants (Prospective studies at Royal Hobart and Launceston General Hospitals)

No	Questionnaire	Answer
1.	a) Do you drink alcohol? If answer "YES", b) What type of alcohol do you like to drink (e.g., beer, wine, spirits)? c) In a week, how many times would you drink and how much would you drink each time?	□ Yes □ No
2.	Do you smoke?	□ Yes □ No
3.	Were you recently hospitalised for any reason? If so, when?	□ Yes □ No
4.	Do you remember any recent changes in drug therapy before your admission at Royal Hobart Hospital? If answer "YES", please recollect the names of the medicines changed.	□ Yes □ No
5.	Are you allergic to any medicines – e.g., Penicillin or Aspirin? If "YES", list the allergy and the reaction.	□ Yes □ No
6.	Within the last three months, have you experienced any 'bad reactions' to any medicines?	□ Yes □ No
7.	Have you taken any OTC medications apart from your regular medications? If "YES", please recollect the names/s of those.	□ Yes □ No
8.	Do you take any complimentary medicines/herbal medicines? If "YES", please recollect the names/s of those.	□ Yes □ No
9.	Do you have a regular community pharmacy? How many pharmacies do you attend for your prescription medications?	□ Yes □ No
10.	Do you usually use dosage administration aids (for example, a dosette box, or Websterpak, where the pharmacy packs your medicines into days and weeks for you)?	□ Yes □ No
11.	a) Do you use different brands of the same medication, sometimes called generic prescription medications?	□ Yes □ No
12.	Have you recently had a Home Medicines Review (pharmacist interviewing you about your medications in your home)/MedsCheck/Diabetes MedsCheck?	□ Yes □ No

Appendix 5. Drug exposure in the study population, n=1008 (Prospective studies at Royal Hobart and Launceston General Hospitals)

Characteristic	Value
ACEIs or ARBs	55.0
Diuretics	49.5
Antiplatelets	47.8
β-Blockers	35.7
Calcium channel blockers	26.7
α-Blocking agents	35.0
Opioids	31.1
Drugs of narrow therapeutic index*	24.4
Psycholeptics**	24.0
Drugs used in diabetes	23.2
Benzodiazepines	20.4
Anticoagulants	20.4
Antibacterials	15.0
Cardiac glycosides	10.9
Antipsychotics	4.6
NSAIDs	4.2
Specific high-risk drugs, %	
Warfarin	12.0
Rivaroxaban	4.7
Amiodarone	2.8
Apixaban	2.2
Dabigatran	1.7
Theophylline	0.2

** Antipsychotics, anxiolytics, hypnotics and sedatives.

* Digoxin, amiodarone, theophylline, phenytoin, carbamazepine and sodium valproate.

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

Appendix 6. Drug classes and drugs causing or contributing to hospital admission due to adverse drug reactions

Drug class	Frequency (%)	Drugs involved (n=452)
Cardiovascular drugs	269 (59.5)	
Diuretics (108)		Furosemide (61), spironolactone (18), hydrochlorothiazide (14), indapamide (13), amiloride (2)
Agents acting on the renin-angiotensin system (74)		Perindopril (19), candesartan (15), irbesartan (13), ramipril (13), telmisartan (6), valsartan (1), quinapril (1), enalapril (3), fosinopril (1), olmesartan (1), trandolapril (1)
β-Blocking agents (32)		Metoprolol (15), atenolol (5), carvedilol (5), bisoprolol (5), sotalol (2)
Calcium channel blockers (22)		Amlodipine (11), felodipine (4), diltiazem (3), verapamil (2), lercanidipine (2)
Vasodilators used in cardiac diseases (9)		Isosorbide mononitrate (8), glyceryl trinitrate (1)
Cardiac glycosides (7)		Digoxin (7)
Antiarrhythmic drugs (4)		Amiodarone (4)
α-Adrenoreceptor antagonists (6)		Prazosin (6)
Lipid modifying agents (5)		Atorvastatin (3), simvastatin (1), rosuvastatin (1)
Other cardiac preparations (2)		Ivabradine (1), macitentan (1)
Drugs acting on the nervous system	100 (22.1)	
Antidepressants (31)		Amitriptyline (14), venlafaxine (3), desvenlafaxine (2), duloxetine (3), citalopram (3), escitalopram (1), paroxetine (1), mirtazapine (2), fluvoxamine (1), sertraline (1)

Drug class	Frequency (%)	Drugs involved (n=452)
Opioids (22)		Buprenorphine (8), oxycodone (7), morphine (3), tramadol (2), codeine (1), tapentadol (1)
Benzodiazepines (19)		Diazepam (6), temazepam (4), nitrazepam (3), oxazepam (3), alprazolam (3)
Antiepileptics (12)		Pregabalin (10), valproate sodium (1), gabapentin (1)
Anti-Parkinson drugs (9)		Levodopa combinations (7), pramipexole (2)
Antipsychotics (7)		Quetiapine (3), prochlorperazine (2), risperidone (1), olanzapine (1)
Antithrombotic agents	31 (6.9)	Acetylsalicylic acid (11), warfarin (7), rivaroxaban (6), clopidogrel (4), enoxaparin (2), apixaban (1)
Immunosuppressants	12 (2.7)	Methotrexate (6), mycophenolate mofetil (1), etanercept (1), tocilizumab (1), thalidomide (1), azathioprine (1), leflunomide (1)
Antineoplastic agents	3 (0.7)	Chlorambucil (1), melphalan (1), hydroxycarbamide (1)
NSAIDs	4 (0.9)	Naproxen (1), ibuprofen (1), diclofenac (1), meloxicam (1)
Drugs for obstructive airway diseases	1 (0.2)	Theophylline (1)
Drugs used for urinary frequency and incontinence	2 (0.4)	Oxybutynin (2)
Thyroid preparations	2 (0.4)	Thyroxine (2)
Drugs for constipation	2 (0.4)	Sodium picosulfate combinations (2)
Antimalarials	2 (0.4)	Hydroxychloroquine (1), quinine (1)

Drug class	Frequency (%)	Drugs involved (n=452)
Drugs used in diabetes	4 (0.9)	Insulin (2), sitagliptin (1), gliclazide (1)
Systemic antibacterials	5 (1.1)	Sulfamethoxazole and trimethoprim (2), flucloxacillin (1), ciprofloxacin (1), doxycycline (1)
Systemic corticosteroids	6 (1.3)	Prednisolone (4), dexamethasone (1), prednisone (1)
Others	9 (2.0)	Naloxone (3), cyproterone (1), magnesium aspartate (1), denosumab (1), zoledronic acid (1), risedronate (1), allopurinol (1)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs.

Appendix 7. Clinical presentations of adverse drug reactions

Type of ADR	n (%)	ADRs causing or contributing to hospital admission (n=328)
Cardiovascular	96 (29.3)	Hypotension/orthostatic hypotension/syncope (78), bradycardia (12), peripheral oedema (2), tachycardia (2), fluid retention (1), ventricular extrasystoles (1)
Neuropsychiatric	72 (20.0)	Dizziness (44), confusion (14), delirium (3), hallucinations (2), falling (2), drowsiness (1), ataxia (1), mental disturbances (1), nervousness (1), delusions (1), disorientation (1), peripheral neuropathy (1)
Renal and genitourinary	50 (15.2)	Acute kidney injury (49), urinary retention (1)
Haematological	35 (10.7)	Haemorrhage (22), anaemia (9), thrombocytopenia (1), leukopenia (1), bruise (1), myelosuppression (1)
Endocrine and metabolic	30 (9.1)	Hyperkalaemia (11), hyponatremia (11), hypoglycaemia (4), hypokalaemia (2), hypocalcaemia (1), hypothyroidism (1)
Gastrointestinal	24 (7.3)	Nausea (8), vomiting (5), anorexia (3), constipation (3), diarrhoea (3), abdominal pain (1), esophagitis (1)
Neuromuscular and skeletal	12 (3.7)	Myalgia (4), weakness (2), arthralgia (1), dyskinesia (1), tremor (1), limb pain (1), myopathy (1) decreased bone density (1)
Hepatic	1 (0.3)	Increased liver enzymes (1)
Dermatological/allergic	2 (0.6)	Rash (1), erythema (1)
Other	6 (1.8)	Infection (5), flu-like symptoms (1)

Appendix 8. The Naranjo adverse drug reaction probability scale

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.				
	Yes	**No**	**Do not know**	**Score**
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction reappear when a placebo was given?	-1	+1	0	
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

The ADR was assigned to a probability category from the total score as follows: definite $\geq$9, probable 5 to 8, possible 1 to 4, doubtful $\leq$0.

a) A "definite" reaction was one that (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2)

followed a recognised response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.

b) A "probable" reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognised response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

c) A "possible" reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognised pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.

d) A reaction was defined as “doubtful" if it was likely related to factors other than a drug.

Appendix 9. Hartwig's adverse drug reaction severity assessment scale

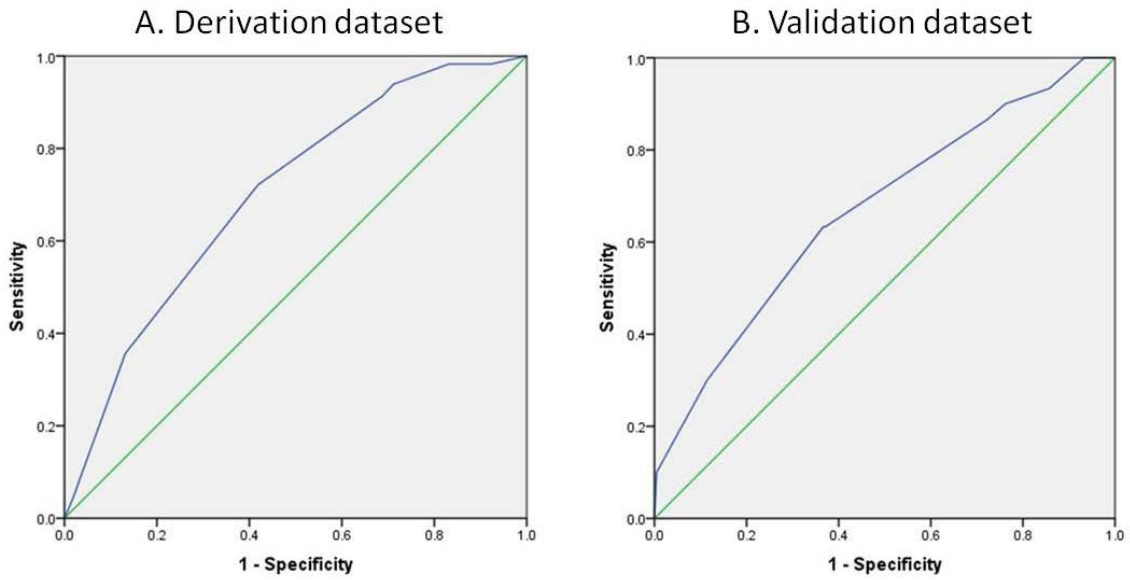
Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required that the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment is required. No increase in length of stay.
Level 3	The ADR required that the suspected drug be held, discontinued, or otherwise changed, **AND/OR** an antidote or other treatment was required. No increase in length of stay.
Level 4	(a) Any level 3 ADR that increases length of stay by at least one day, **OR** (b) The ADR was the reason for admission.
Level 5	Any level 4 ADR that requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.

Mild = Levels 1 and 2

Moderate = Levels 3 and 4

Severe = Levels 5, 6 and 7

Appendix 10. Receiver operator characteristic curve for the derivation (Royal Hobart Hospital) dataset (A) and the validation (Launceston General Hospital) dataset (B)



The area under the curve are 0.70 (95% CI 0.65–0.75) and 0.67 (95% CI 0.56–0.78) for the derivation and validation datasets respectively.

Appendix 11. A box plot of PADR-EC scores by readmission status